Health Technology Assessment 2002; Vol. 6: No. 6

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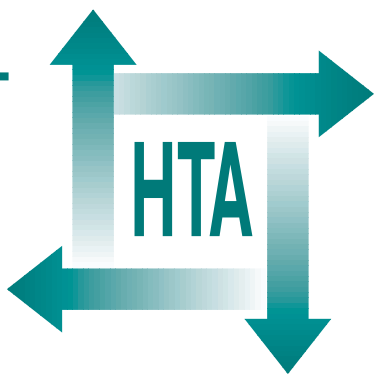
Health Technology Assessment
NHS R&D HTA Programme



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The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment

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Competing interests: Professor Peter Kopelman, a member of the expert panel, has undertaken clinical trials in obese participants for Knoll Limited

Published April 2002

This report should be referenced as follows:

O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G. The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment. *Health Technol Assess* 2002;**6**(6).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

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The research reported in this monograph was funded as project number 00/05/02.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

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Contents

List of abbreviations

AE	adverse events*
AEE	adrenaline-stimulated energy expenditure*
ANCOVA	analysis of covariance*
ANOVA	analysis of variance
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CHD	coronary heart disease
CI	confidence interval
DB	double blind*
DBP	diastolic blood pressure
df	degrees of freedom
EE	energy expenditure*
FPG	fasting plasma glucose
HbA_{1c}	glycosolated haemoglobin concentration*
HDL	high-density lipoprotein*
HDL-C	high-density lipoprotein cholesterol
HR	heart rate*
ITT	intention-to-treat
LDL	low-density lipoprotein*
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
NA	not applicable*
ns	not significant*
NS	not stated*
OR	odds ratio*
PP	per protocol*
PR	pulse rate*
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REE	resting energy expenditure*
RMR	resting metabolic rate*
RR	relative risk
SAE	serious adverse event*
SB	single blind*
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean*
SF-36	Medical Outcome Study 36-item short form health survey[57]
VAS	visual analogue scale
VLCD	very-low-calorie diet
WMD	weighted mean difference

* Used only in tables

Executive summary

Background

The prevalence of obesity in developed societies is increasing. Obesity is associated with an increased risk of co-morbidity, including cardiovascular disease and diabetes. Following the withdrawal of fenfluramine and dexfenfluramine in 1997, interest has focused on a novel anti-obesity drug: sibutramine. (Note: since the completion of this review, phentermine has been withdrawn from the market – May 2001.)

Aims of the review

To assess systematically the clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity.

Methods

Search strategy

A total of 19 electronic databases were searched from inception to June 2000. Additionally, Internet searches were carried out, bibliographies of retrieved articles were examined, and a submission was received from the manufacturer of sibutramine.

Inclusion and exclusion criteria

Randomised controlled trials (RCTs) evaluating the effectiveness of sibutramine used for weight loss or maintenance of weight loss in overweight or obese patients were eligible for inclusion. Primary outcome measures were changes in body weight, fat content or fat distribution. Secondary outcomes were changes in obesity-related risk-factor profiles, such as lipid levels, indicators of glycaemic control and blood pressure. Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa were excluded.

Process of study selection

The assessment of titles and abstracts was performed independently by two reviewers. If either reviewer considered a reference to be relevant, the full paper was retrieved. Two independent reviewers assessed full papers against the review selection criteria. Disagreements were resolved through discussion.

Data extraction

Data were extracted by one reviewer into structured summary tables and checked by a second reviewer. Any disagreements about data were resolved by discussion.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. Quality assessment was performed independently by two reviewers, with disagreements resolved by discussion.

Methods of analysis/synthesis

This report is a narrative summary, with results grouped according to study endpoint. Statistical pooling was undertaken in groups of trials that were considered to be sufficiently similar.

Estimation of quality of life, costs and cost-effectiveness and/or cost per quality-adjusted life-year (QALY)

Relevant economic evaluations were identified from the search strategy described above. Assessment of methodological quality was undertaken using principles outlined in published guidelines.

Company submission

Data provided by the manufacturer of sibutramine were subject to the same selection and appraisal processes as other studies considered for inclusion in the review, except that only RCTs with a duration of at least 1 year were selected.

Results

Results of the search strategy

A total of 16 RCTs (11 published and five submitted by the manufacturer) and one economic evaluation (submitted by the manufacturer) were included in the review. (Note: since the completion of this review, two of the RCTs submitted by the manufacturer have been published.)

Results of the quality assessment

The methodological quality of trials was moderate to good. The main problems were lack of detail on methods used to produce true randomisation,

small sample sizes, and failure to use intention-to-treat analysis.

Evidence of clinical effectiveness and cost-effectiveness

Most of the individual placebo-controlled trials and pooled estimates suggested that sibutramine produced statistically significant greater weight loss than placebo at all observed endpoints (weighted mean difference for weight change at 8 weeks: –3.4 kg; mean difference range for weight change at 6 months: –4.0 to –9.1 kg; and at 1 year: –4.1 to –4.8 kg). The most frequent dosing regimen was 10–20 mg daily. Findings suggested a dose–effect relationship in terms of weight loss. Sibutramine was also associated with better weight maintenance relative to placebo (statistically significant difference). Results from mainly small trials showed that sibutramine produced more favourable outcomes in terms of loss of fat mass, reduction in body mass index and loss of at least 5% and 10% of initial body weight. Between-group differences for waist circumference, hip circumference and waist–hip ratio did not reach statistical significance in most trials. Similar results for weight loss were found in trials recruiting solely patients with type-2 diabetes; between-group differences for changes in indicators of glycaemic control were not usually statistically significant. Sibutramine use was associated with small, statistically significant increases in pulse rate, heart rate and blood pressure. The cost per QALY was estimated as £10,500.

Conclusions

Implications for clinical practice

Although many trials demonstrated statistically significant differences between groups in terms of weight loss in favour of sibutramine versus placebo, the differences may not always be of clinical significance. The clinical significance of between-group differences for secondary outcomes may also be debatable. Possible adverse effects should be taken into account when prescribing sibutramine.

Recommendations for future research

Future trials should ensure good methodological quality, including adequate statistical power and analysis by intention-to-treat. Further research is required to determine the effects of sibutramine in different patient groups according to gender, age, ethnicity and social class. Clinical trials should be designed to match protocols observed in clinical practice with regard to patient selection and treatment.

Chapter 1
Background

The prevalence of obesity

Epidemiological surveys in England indicate that the prevalence of obesity, defined as a body mass index (BMI) of greater than 30 kg/m^2,[1] is increasing.[2–4] In 1994, it was estimated that, for those people aged over 16 years, 44% of men were classified as overweight (BMI > 25–30 kg/m^2) and 13% were classified as obese (BMI > 30 kg/m^2). For women the figures were 31% and 16%, respectively. In 1998, the respective figures had risen to 46% and 17% in men, and 32% and 21% in women.[4] Projected figures for prevalence (both sexes) in the year 2000 are 50% and 20%, respectively.[5]

Those at risk of becoming obese

It is deemed that large sections of the population in developed societies are at risk of developing obesity.[6] Those people considered to be particularly at risk include Asian people,[7] children from families where one or both parents are overweight or obese[8–10] and those giving up smoking.[11] High birth weight may also be associated with an increased risk of obesity later in life.[10]

The risk of obesity is associated with social class (defined as social class of head of household) and household income. In 1998, it was estimated that 14% of women in social class I were obese, compared with 18% in social class III (non-manual) and 28% in social class V. However, the pattern of association was less clear for overweight women and for both obese and overweight men. In terms of household income, the prevalence of obesity in both sexes decreases as income increases. The relationship between income and being overweight in both sexes is less clear. These data are age-standardised.[4] Findings from a systematic review of childhood predictors of adult obesity showed that there is a link between low socioeconomic status in early life and obesity in adulthood.[10]

The risk of becoming obese increases with age, up to a certain point, in both sexes. In 1998, it was estimated that 16% of men aged 25–34 years were obese, compared with 23% aged 55–64 years. For women, the respective figures were 16% and 29%. It should be noted, however, that the BMI tends to decrease in older people. This decline begins between 65 and 74 years in men, and from 75 years onwards in women.[4] It is also thought that men and women are at greater risk of becoming obese at certain points in the life cycle, with an increased risk for men during the late 30s. Women may be more vulnerable when entering marriage, during pregnancy, during the menopause and at retirement.[1]

Health risks of obesity

Health risks of obesity include increased risk of coronary heart disease (CHD), hyperlipidaemia, hypertension, diabetes, cholelithiasis, degenerative joint disease, social and psychological problems,[12] and obstructive sleep apnoea.[13–16] More specifically, there is a link between android or abdominal obesity and CHD, hypercholesterolaemia, hypertension and diabetes.[17–19]

It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in blood pressure (BP), cholesterol and triglycerides achievable with a 5–10% reduction in initial body weight.[20] In order to obtain long-term health benefits, however, weight loss must be maintained. Concern has been expressed over weight cycling (or 'yo-yo dieting') whereby some individuals alternate between periods of weight loss and weight regain. However, the association between weight cycling and morbidity remains unclear.[21–25]

Measurements of obesity

Definitions of the terms 'overweight' and 'obesity' vary between studies. The BMI (body weight in kg divided by the height in m^2) is frequently used as a method of classification in research, clinical practice and public health settings (*Table 1*). However, the BMI does not take into account factors such as size of body frame, proportion of lean mass, gender and age. Measures of central obesity, such as waist circumference, are considered to be better predictors of cardiovascular

TABLE I *Classification of weight according to BMI level*[26]

WHO classification	BMI (kg/m^2)	Risk of co-morbidities
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0–29.9	Mildly increased
Obese	≥ 30.0	
Class I	30.0–34.9	Moderate
Class II	35.0–39.9	Severe
Class III	≥ 40.0	Very severe

risk.[17] Other measurements include body weight, percentage over ideal body weight, skinfold thickness and other more detailed measures of body composition such as densitometry.

Options for the management of obesity

A range of interventions are available for the management of overweight and obese patients. These include work/school/community programmes (for primary prevention), dietary modification, exercise programmes, behaviour modification programmes, pharmacological agents, commercial programmes (e.g. Weight Watchers) and alternative therapies. Surgery is usually reserved for those suffering from very severe obesity (BMI greater than 40 kg/m^2), for whom less invasive methods of weight loss have failed. The various weight management strategies may be used alone or in combination. A number of literature reviews have covered the broad range of interventions available,[27–30] and recent reports have offered guidelines for the management of obesity.[28,31]

Pharmacological agents used to treat obesity

In 1997, dexfenfluramine and fenfluramine were withdrawn by the manufacturer due to reported cases of valvular heart disease.[32] Following this event, interest in a novel anti-obesity agent, sibutramine, was intensified.

Sibutramine

Sibutramine (Reductil®) is produced by Knoll Limited (Nottingham, UK). It was approved by the Food and Drug Administration in the USA in November 1997 for the treatment of obesity, and was licensed in the UK in May 2001 for the same indication. It is a norepinephrine and serotonin reuptake inhibitor. Sibutramine is indicated in the management of patients with a BMI of 30 kg/m^2 or more (and no associated co-morbidity), or in those with a BMI of 27 kg/m^2 or more in the presence of other risk factors such as type-2 diabetes or hypercholesterolaemia.[33]

Sibutramine increases BP in some patients and therefore regular monitoring is required. Contraindications include the following: history of major eating disorders, psychiatric illness, Gilles de la Tourette syndrome, history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmias, cerebrovascular disease, uncontrolled hypertension, hyperthyroidism, prostatic hypertrophy, phaeochromocytoma, angle closure glaucoma, history of drug or alcohol abuse, pregnancy and breastfeeding. Most frequent adverse effects include dry mouth, insomnia, constipation, nausea, tachycardia, palpitations, hypertension, vasodilation, light-headedness, paraesthesia, headache, anxiety, sweating and taste disturbance. A rare adverse effect is blurred vision.[33]

Other drugs

Orlistat (Xenical®) is produced by Roche Products Limited, Welwyn Garden City, UK. The parent company is Hoffmann-La Roche. It has been licensed in the UK since September 1998 as an anti-obesity drug, and was approved by the Food and Drug Administration in April 1999. Orlistat is an inhibitor of gastric and pancreatic lipases, and inhibits the hydrolysis of dietary triglycerides, consequently limiting the absorption of monoglycerides and free fatty acids. Orlistat is indicated for patients with a BMI of ≥ 30 kg/m^2, or ≥ 28 kg/m^2 or more in the presence of other risk factors (e.g. hypertension, diabetes, hyperlipidaemia).[33]

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, in pregnancy or while breastfeeding. Adverse effects include liquid oily stools, faecal urgency, flatulence and, less frequently, abdominal and rectal pain, headache, menstrual irregularities, anxiety and fatigue.[33]

Orlistat is licensed for use with a mildly hypocaloric diet. Treatment should only be initiated in patients who have achieved a weight loss of at least 2.5 kg in 4 weeks using a dietary programme alone. Orlistat treatment should be discontinued after 3 months if patients lose less than 5% of their initial body weight (calculated from start of treatment), and should be discontinued after 6 months if patients lose less than 10% of initial body weight. Treatment should not usually continue beyond 1 year and never beyond 2 years.[33,34] The National Institute of Clinical Excellence (NICE) guidance on orlistat and sibutramine is available from the NICE website (www.nice.org.uk).

The bulk-forming agent methylcellulose (Celevac®; Shire, UK) is deemed to reduce food intake by producing a feeling of satiety. However, there is little evidence to support this claim. Patients taking this drug must be advised to maintain an adequate fluid intake. Contraindications to use are difficulty in swallowing, gastrointestinal obstruction, colonic atony and faecal impaction. Adverse effects include flatulence, abdominal distension and gastrointestinal obstruction or impaction.[33]

Another drug, phentermine, was licensed in the UK for the treatment of obesity until May 2001, when it was withdrawn from the market, after the completion of this review.

This review will not assess the effectiveness of methylcellulose. A rapid and systematic review assessing the clinical effectiveness and cost-effectiveness of orlistat has been presented in a separate report.[35]

It is generally agreed that pharmacological agents are unsuitable for use as a sole treatment but rather should be employed as an adjunct to other weight-loss interventions such as a prescribed diet, exercise or behavioural therapy. Published guidelines for the management of obesity from the Royal College of Physicians and the Scottish Intercollegiate Guidelines Network (SIGN) endorse this view,[28,31] as do prescribing guidelines.[33] Further recommendations from the Royal College of Physicians state that anti-obesity drugs should not be prescribed for longer than 12 weeks initially. After this time, weight loss should be assessed and therapy should be discontinued in patients who have not achieved at least 5% reduction of initial weight. Prescription may be continued beyond this period for patients attaining at least 5% loss of initial body weight, provided body weight is continually monitored and weight is not regained.[31]

At present, drugs are not normally used for childhood obesity because of the risks of growth suppression. Most of the research literature has so far reflected their use in adults aged up to 75 years.[27]

Aim of the review

To assess systematically the clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity. In this context, the term 'management' covers both weight loss and weight maintenance programmes. The review will consider both overweight and obese people, and the main outcomes of interest will be those reflecting changes in body weight, fat content, or fat distribution. Other relevant health-related outcomes are considered.

Chapter 2
Methods

Search strategy

The following electronic databases were searched from inception to the end of June 2000 to locate information on the clinical effectiveness and cost-effectiveness of sibutramine (using both generic and brand names) in the treatment of obesity:

- Allied and Complementary Medicine database (AMED)
- BIOSIS
- British Nursing Index
- CINAHL
- Cochrane Library CD-ROM (2000 issue 2)
- DARE
- DH-Data
- EconLIT
- EMBASE
- HEED
- HELMIS
- HTA database
- Index to Scientific and Technical Proceedings
- King's Fund Database
- MEDLINE
- National Research Register (NRR) (2000 issue 1)
- NHS EED
- Science Citation Index
- Social Sciences Citation Index.

The search strategy used is provided in appendix 1.

In addition, searches were carried out on the Internet using the manufacturer's website (http://www.4meridia.com), pharmaceutical databases such as PharmInfo Net (http://www.pharminfo.com) and RxList (http://www.rxlist.com), biomedical search engines such as OMNI (http://www.omni.ac.uk), meta-search engines such as The BigHub.com (http://www.thebighub.com) and general search engines such as AltaVista (http://www.altavista.com).

The reference lists of relevant reviews and included trials were checked in order to identify further eligible evaluations. When relevant conference abstracts were identified, authors were contacted and requested to provide a full report (for trials) or a bibliography (for reviews).

In addition, material was submitted from the manufacturer of sibutramine.

Inclusion and exclusion criteria

In order to be included in the review, studies had to fulfil criteria relating to study design, participant characteristics, interventions and outcomes.

Study design

Randomised controlled trials (RCTs), incorporating any duration of therapy and any length of follow-up, were considered for inclusion in the review.

Participants

The following were included in the review:

- RCTs recruiting participants defined as being overweight or obese
- RCTs recruiting participants wishing to maintain weight loss, having been previously overweight or obese.

Trials involving specific patient groups such as those with diabetes, hypertension or hyperlipidaemia were included in the review, provided they met the above criteria.

Definitions of obesity and of being overweight varied between studies. Studies recruiting participants who were not overweight or obese but who wished to achieve weight loss were excluded. Evaluations for which mixed participants were recruited (e.g. some with healthy weights, some overweight/obese) were included if results were presented separately for the overweight/obese patients.

Studies recruiting people with eating disorders such as anorexia nervosa and bulimia nervosa were excluded. In trials where overweight/obese participants were recruited as well as those with the above eating disorders, only those where results were presented separately for the overweight/obese participants were included.

Interventions

Evaluations of sibutramine used to treat overweight/obese patients or to maintain weight

loss in previously overweight/obese patients were considered for inclusion in the review. Sibutramine could be combined with other strategies such as dietary restriction or behavioural programmes. Participants in control groups could receive placebo, an alternative anti-obesity pharmacological agent or an alternative anti-obesity intervention (e.g. based on dietary regimen, physical activity or behavioural modification).

Outcomes

The primary outcome of the review was an assessment of obesity/overweight status measured as changes in body weight, fat content or fat distribution:

- measures of weight change include absolute weight change and percentage weight change relative to baseline
- measures of fat content include BMI, ponderal index, skinfold thickness, fat-free mass and fat change
- measures of fat distribution include waist size, waist–hip ratio and girth–height ratio.

In order to be included, trials had to report measurements at baseline and post-intervention.

The secondary outcomes of the review included physiological changes occurring in association with changes in body weight/fat content/fat distribution. The most common examples of these were changes in lipid profiles, glycaemic control among those with diabetes, and BP among those with hypertension. Where available, data were recorded on patient-related quality of life (QoL).

Data on adverse effects and costs were also recorded, where available.

Language restrictions

Only studies published in English, French, Dutch or German were considered for inclusion in the review.

Process of study selection

All titles and abstracts were assessed independently by two reviewers. If either reviewer considered a reference to be potentially relevant, a hard copy of the paper was retrieved for further consideration. Full papers were assessed against the selection criteria detailed above (see the prescreen form in appendix 2). Prescreening was performed independently by two reviewers. Disagreements were resolved through discussion or by recourse to a third reviewer.

Data extraction

The following data were extracted from each included trial: author(s), year of publication, country of study, study aim, method of randomisation, outcomes measured, setting of treatment, duration of treatment and follow-up, participant selection criteria, baseline comparability of groups, intervention characteristics, results per treatment arm, incidence of adverse effects and numbers of/reasons for withdrawal. Data were extracted by one reviewer into standardised, structured tables, (see appendix 3) and were checked by a second reviewer. Any disagreements about data were resolved through discussion. Where multiple publications of the same evaluation were identified, all publications were examined to ensure that all relevant data for that study were recorded and data were then presented as a single entry.

Quality assessment

Each included trial was assessed against a comprehensive checklist for methodological quality. The following aspects of quality were assessed: method of randomisation, participant selection criteria, sample size, comparability of treatment arms, blinding, statistical analysis and description of withdrawals (appendix 4). Quality assessment was performed independently by two reviewers with disagreements resolved through discussion.

Methods of analysis/synthesis

A narrative summary of results has been presented here, with results grouped according to study endpoint and type of weight-management programme (weight loss or weight maintenance). Statistical pooling (meta-analysis) has been undertaken for groups of trials that were considered to be sufficiently similar. For continuous data, a pooled weighted mean difference (WMD) was generated and, for dichotomous variables, a summary relative risk (RR) was calculated.

The WMD is a method of meta-analysis used to combine measures on continuous scales (e.g. body weight) where the mean, standard deviation (SD) and sample size in each group are known. The weight given to each study (i.e. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate

of effect and, in the statistical software in RevMan (as used in this review), is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.[36]

The RR is the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1.0 indicates no difference between comparison groups. For undesirable outcomes, an RR < 1.0 indicates that the intervention was effective in reducing the risk of that outcome.[36] In this review, the summary RR was calculated in terms of the risk of failure to achieve 5% or 10% loss of initial body weight.

A random-effects model was employed for both WMD and RR, and 95% confidence intervals (95% CIs) were presented with the central-effect estimates. The results of related statistical tests for heterogeneity have been presented with each analysis. Statistically significant heterogeneity was considered to be present when the associated *p*-value was < 0.10. The meta-analyses were generated using Metaview v. 4.1 (Review Manager v. 4.1, 2000; The Cochrane Collaboration).

Estimation of QoL, costs and cost-effectiveness and/or cost per quality-adjusted life-year

The following specialist sources were searched to identify relevant economic literature: EconLIT, NHS EED and HEED. Identified economic evaluations were submitted to the same study selection and data extraction process as studies of clinical effectiveness. Assessment of methodological quality was undertaken using principles outlined in published guidelines.[37]

Company submission

Data from the company submission were subject to the same selection and appraisal processes as other studies considered for inclusion in the review. The sole exception to this was that only RCTs with a duration of at least 1 year were selected. This *post hoc* decision was taken in light of the time constraints of this review.

Chapter 3
Results

Results of search strategy

The search strategy (see chapter 2 and appendix 1) generated 658 references of possible relevance to this review. Once titles (and abstracts, where available) had been assessed, hard copies of 187 papers were examined (please note that these figures relate to the joint review of the two drugs orlistat and sibutramine). In all, 16 RCTs[38–53] and one economic evaluation[54] were included. The economic evaluation and five of the RCTs were submitted by the manufacturer of sibutramine.[49–54] Details of included trials are summarised in appendix 3. Since the completion of this review, two trials from the company submission[50,51] have been published.[55,56]

Quality assessment

Published RCTs (appendix 4)

A total of 11 published trials were included.[38–48] Of these, three reported using methods to produce true randomisation;[41,42,48] in other trials, the method of randomisation was not stated. Since all the trials were described as 'double-blind', it was assumed that concealment of randomisation was carried out. However, most trials did not report the methods used to achieve this. All trials reported participant selection criteria, although only briefly in one case.[38] Four RCTs reported using an *a priori* power calculation for sample size;[42,46–48] in one the calculated numbers were not recruited;[44] in four it was not stated;[38,39,41,43] and in two it was unclear.[40,45] In terms of the number of participants allocated per treatment arm, 20 or fewer patients were recruited in four trials,[38–40,43] between 20 and 50 in two trials,[44,48] between 50 and 100 in three trials,[42,46,47] and more than 100 in two trials.[41,45]

All trials reported baseline comparability of treatment groups, expressed an intention to provide identical treatment to groups apart from the drugs under study, and indicated blinding of patients by use of placebo or an alternative drug that was matched in appearance to the study drug. In all trials it was unclear whether caregivers and outcome-assessors were blinded. That is to say, all trials were defined as 'double-blind'; however, it was not explained in any study whether the caregivers and outcome-assessors were the same personnel. None of the trials reported procedures to check whether blinding had been successful.

All trials gave details of the statistical methods used, and all but two[41,47] provided results in terms of central values with variance. In most of the trials, adjustment for imbalance of baseline variables was not required because study groups appeared to be comparable. There were two exceptions to this. In one trial, a statistically significant ($p < 0.05$), although possibly not clinically significant, overall difference in baseline BMI was detected.[41] In a second trial, an imbalance of the distribution of ethnic groups was noted, with more Caucasians in the sibutramine group ($p = 0.022$).[48] Neither of these trials provided details of the methods used to adjust for baseline imbalance. Seven trials described the methods used to take account of missing data;[41,42,44–48] while in one trial this was not applicable since there were no withdrawals and therefore no missing data.[43] Seven trials analysed by intention-to-treat (ITT);[41,42,44–48] in one trial this was not applicable because there were no withdrawals;[43] it was not stated for another;[40] and was not undertaken for two.[38,39]

Seven trials reported numbers of withdrawals per treatment group with reasons;[40,41,44–48] one reported the numbers per group but not with reasons;[42] two provided numbers according to reason for withdrawal, but not per group;[38,39] and for one there were no withdrawals.[43] Patient adherence with the study regimen was assessed in eight trials,[39,40,42–46,48] but this was not stated in three.[38,41,47]

RCTs from the company submission

Five trials were included from the company submission.[49–53] All the trials failed to report the following: method of randomisation, use of an *a priori* power calculation for sample size, and baseline group comparability. All used concealed randomisation and all reported selection criteria for participants. One trial recruited between 60 and 70 participants per treatment arm,[53] whilst the other four recruited over 100 participants per group. All indicated intention to provide identical treatment to participants, with the exception of study medication, and all involved blinding of

patients. For all trials, it was unclear whether caregivers and outcome-assessors were blinded, and none reported using procedures to check whether blinding had been successful. All reported the statistical methods used, but none reported variance associated with central estimates. None of the trials stated whether adjustments had been made for baseline imbalance. Three described methods for dealing with missing data,[49,50,53] and all reported withdrawals. Four trials performed ITT analyses[49,50,52,53] and in one this was not stated.[51] None reported assessment of patient adherence with the study regimen.

Since the completion of this review, two trials from the company submission[50,51] have been published.[55,56] The information described in this report is based on details provided by the manufacturer at the time that the review was being prepared.

Results from RCTs

The most important findings have been outlined in the text of the review. The reader may also refer to the data extraction tables (appendix 3) for more detailed information; for example, to see specific values in connection with study outcomes, where these are not mentioned in the text. Where results are reported as 'significant' this refers to statistical significance (as opposed to clinical significance) unless otherwise stated.

A total of 11 published trials of sibutramine were identified.[38–48] Results were reported for different endpoints: 8 weeks,[38–40] 12 weeks,[43–45] 6 months[41,42,47,48] and 1 year (weight maintenance).[46] In addition, five RCTs were included from the company submission.[49–53]

RCTs with an 8-week endpoint

Three small trials had an 8-week endpoint.[38–40]

Hansen et al., *1999*[38]

In one trial, obese, otherwise healthy patients were recruited, who had maintained a stable weight during the 3 months prior to the study.[38] No dietary restrictions were imposed, and patients were instructed not to change their food intake or levels of physical activity. They were randomised to receive either sibutramine 15 mg/day or placebo for 8 weeks.

Patients in the sibutramine group achieved significantly greater mean weight loss compared to placebo (loss of 2.6 kg versus gain of 0.4 kg, $p < 0.001$). A similar pattern of results was seen for change in fat mass (–2.2 kg versus –0.2 kg, $p < 0.001$) and change in fat-free mass (–1.5 kg versus +0.2 kg, $p < 0.001$). In addition, patients taking sibutramine reported significantly decreased hunger and anticipated food consumption, and increased satiety.[38]

Adverse events and withdrawals

Significantly greater increases in heart rate and diastolic BP (DBP) were observed in the sibutramine group relative to placebo ($p < 0.001$ and $p < 0.05$, respectively); however, no significant between-group differences were observed for changes in systolic BP (SBP). Two patients withdrew from the trial due to adverse effects: one had a migraine, and the other had a cold. The treatment allocation of these patients was not reported.[38]

Seagle et al., *1998*[39]

In a second trial, participants within the age range 18–45 years with a BMI between 28 and 40 kg/m^2 were included.[39] All patients were instructed to follow a 1200 kcal/day diet containing 50% of energy from carbohydrates, 30% from fat and 20% from protein. They were encouraged to be more physically active but no specific regimen or goal was given. Patients were randomly allocated to groups receiving sibutramine 30 mg/day or sibutramine 10 mg/day or placebo for 8 weeks. This trial also included a weight-maintenance component. The drugs were discontinued after 8 weeks and diet alone was used with the intention of maintaining patients at their week-8 body weights for an additional 4 weeks.

At both the 10 mg/day and 30 mg/day doses, sibutramine achieved significantly greater weight loss compared with placebo ($p < 0.001$). The mean values for weight change at 8 weeks were: –7.4 kg (30 mg dose), –7.1 kg (10 mg dose) and –3.3 kg (placebo). Similar results, at 8 weeks, were seen for change in fat mass: –5.2 kg (30 mg dose), –4.3 kg (10 mg dose) and –3.0 kg (placebo) ($p < 0.05$ for both sibutramine groups versus placebo); and change in fat-free mass: –2.4 kg (30 mg dose), –2.3 kg (10 mg dose) and –0.3 kg (placebo) ($p < 0.05$ for both sibutramine groups versus placebo). In all, 93% of participants in the 30 mg group lost more than 5% of their baseline body weight. The figures were 80% for the 10 mg group and 27% for the placebo group. The values for greater than 10% loss from baseline were 28%, 33% and 0%, respectively. Body composition was determined from measurements of body density estimated by underwater weighing.[39]

At both the 10 mg/day and 30 mg/day doses, sibutramine achieved significantly greater reductions in BMI compared with placebo ($p < 0.05$). The mean values for change in BMI at 8 weeks were: –2.7 kg/m^2 (30 mg dose), –2.6 kg/m^2 (10 mg dose) and –1.2 kg/m^2 (placebo). No statistically significant differences were found between groups for change in waist circumference or change in waist–hip ratio. Both sibutramine groups produced significantly greater mean reductions in hip circumference compared with placebo ($p < 0.05$). The mean changes at 8 weeks in the 10 mg and 30 mg groups were both –5.2 cm, and –2.0 cm for placebo.[39]

No significant treatment effects were observed for evening hunger, evening satiety, sweet food craving, savoury food craving, carbohydrate craving or carbohydrate snacking. However, a significant decrease in overall appetite at 8 weeks (assessed using a visual analogue scale; VAS) was seen in the 30 mg group versus the other two groups ($p = 0.009$).[39]

In terms of maintaining the body weight achieved at 8 weeks using diet alone, the between-group differences (either dose of sibutramine versus placebo) remained statistically significant in favour of sibutramine for change in body weight and change in BMI at 12 weeks (both $p < 0.05$). However, the significant between-group differences observed at 8 weeks for change in fat mass and change in fat-free mass were no longer statistically significant at 12 weeks. The between-group difference for mean change in waist circumference was statistically significant between sibutramine 10 mg and placebo ($p < 0.05$), and the between-group difference for change in hip circumference was statistically significant between sibutramine 30 mg and placebo ($p < 0.05$). The between-group difference in waist–hip ratio remained non-significant at 12 weeks. All outcomes at 12 weeks were assessed relative to baseline values.[39]

Adverse events and withdrawals

The most frequently reported adverse events in the sibutramine groups were anorexia, nausea, central nervous system stimulation, dizziness, dry mouth, insomnia and rhinitis. No adverse effects were noted for laboratory parameters, vital signs or ECG readings. There were no withdrawals due to adverse events, and most were reported as being mild or moderate in severity.[39]

Weintraub et al.*, 1991*[40]

For the third trial, participants within the age range 18–65 years weighing 130–180% of the ideal body weight were recruited. Women of child-bearing potential were excluded. All participants underwent a 3-week run-in period, when a dietary regimen was initiated, based on 22–25 kcal/kg ideal body weight/day. This diet continued throughout the 8-week double-blind treatment phase, for which patients were randomised to sibutramine 20 mg/day, sibutramine 5 mg/day or placebo.[40]

The values for mean weight change at 8 weeks (measured from the start of randomisation) were –5.0 kg (20 mg dose of sibutramine), –2.9 kg (5 mg dose) and –1.4 kg (placebo), with statistically significant differences between both the active treatment groups and placebo, and also between the two different doses of sibutramine ($p < 0.05$ for all comparisons). Results of regression analysis suggested a significant dose–effect relationship between weight loss and dose of sibutramine.[40]

Adverse events and withdrawals

No clinically significant changes were observed in pulse, BP or ECG parameters during the course of the study. However, an increase in heart rate was observed in all groups between baseline and week 8. Patients receiving sibutramine 20 mg/day reported increased frequency of headaches. One patient in the sibutramine 5 mg group and seven in the 20 mg group reported sleep difficulty and six patients in the 20 mg group reported irritability. Five patients in the placebo group, six in the 5 mg group and six in the 20 mg group complained of dry mouth. Skin reactions (rash or dryness) occurred equally across the groups.[40]

Five patients withdrew due to adverse events. One patient receiving placebo had a skin rash and hives, and one patient in the 5 mg group experienced headache, dizziness, nausea, abdominal cramps and faintness. Three patients in the 20 mg group withdrew: one due to depression, fatigue, headache and early morning wakening; one due to abdominal pain, heartburn and gas; and one due to rash, panic attacks, numbness, and tingling of hands and feet.[40]

Pooled analyses for 8-week endpoint

The above three trials were pooled for change in body weight at 8 weeks for sibutramine doses within the range 10–20 mg/day versus placebo.[38–40] A statistically significant difference was found in favour of sibutramine. The summary WMD (random-effects model) was –3.4 kg (95% CI, –4.22 to –2.58; $p < 0.00001$, chi-squared test for heterogeneity 0.70, df (degrees of freedom) = 2, $p = 0.71$) (*Figure 1*).

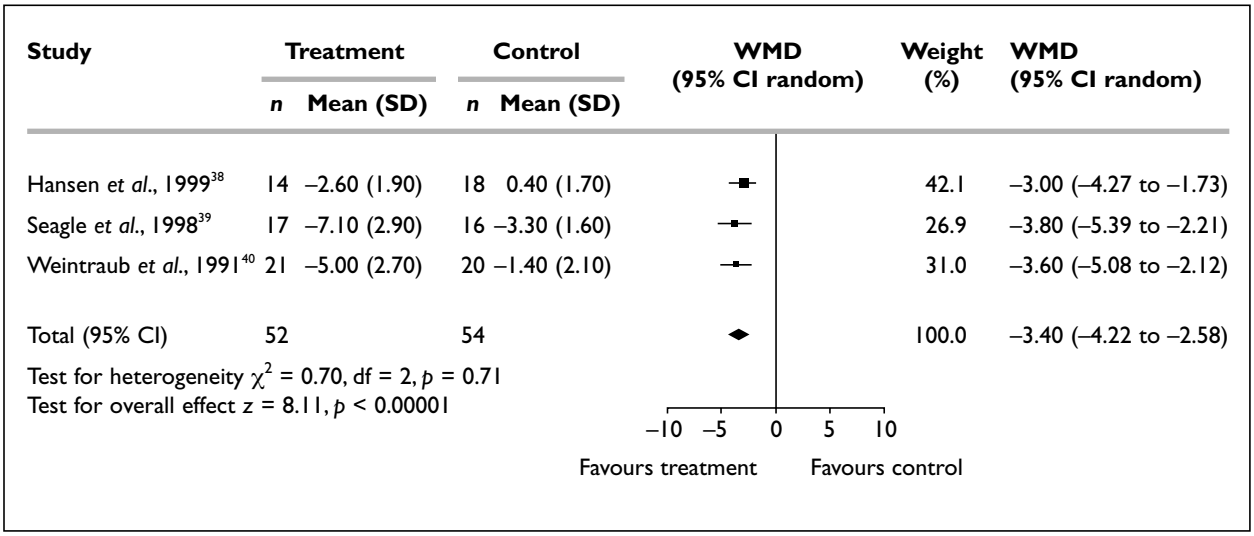

FIGURE 1 *Change in body weight at 8 weeks (kg) for sibutramine 10–20 mg/day versus placebo*

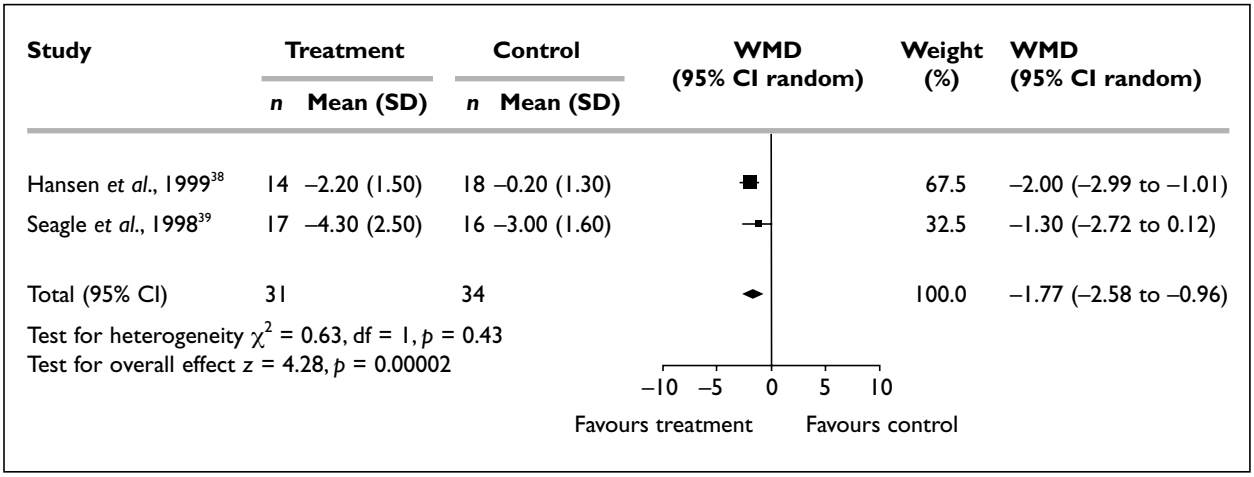

FIGURE 2 *Change in fat mass at 8 weeks (kg) for sibutramine 10–20 mg/day versus placebo*

Two of the trials were pooled for change in fat mass at 8 weeks for sibutramine doses within the range 10–20 mg/day versus placebo.[38,39] Again, a statistically significant difference was found in favour of sibutramine. The WMD was –1.77 kg (95% CI, –2.58 to –0.96; $p < 0.00002$, chi-squared test for heterogeneity 0.63, df = 1, $p = 0.43$) (*Figure 2*).

Sibutramine-treated patients also lost more fat-free mass: WMD –1.83 kg (95% CI, –2.48 to –1.19; $p < 0.00001$, chi-squared test for heterogeneity 0.21, df = 1, $p = 0.65$) (*Figure 3*).[38,39]

RCTs with a 12-week endpoint

Three trials reported results at 12 weeks.[43–45]

Finer et al., *2000*[44]

In the first trial, patients with a diagnosis of type-2 diabetes for at least 6 months were eligible for inclusion. Additionally, participants had to be aged 30–65 years and have a BMI greater than 26 kg/m^2. During a 1-week run-in period, all patients commenced an individualised, reduced calorie diet, with an energy deficit of 500 kcal/day. This continued throughout the 12-week trial, during which patients were randomised to receive sibutramine 15 mg/day or placebo.[44]

All changes were assessed relative to baseline values. When compared with placebo, sibutramine produced significantly greater mean weight loss (–2.4 kg versus –0.1 kg, $p < 0.001$) and a greater reduction in BMI (–0.9 kg/m^2 versus –0.1 kg/m^2, $p < 0.001$). Overall, 19% of patients in the sibutramine group lost more than 5% of their baseline weight compared with none in the placebo group ($p < 0.001$). Analysis of body composition showed that sibutramine-treated patients lost significantly more fat mass than placebo participants

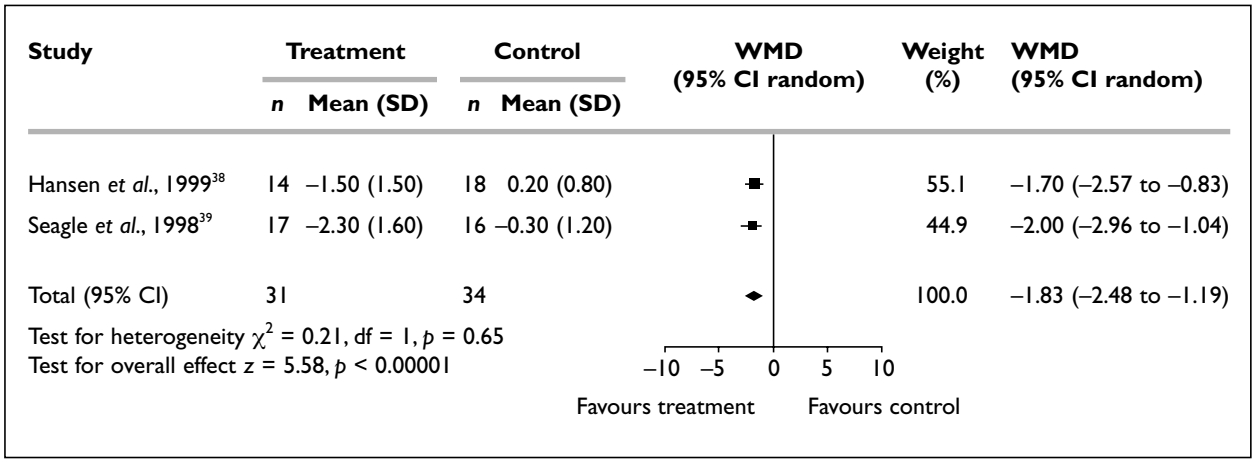

FIGURE 3 *Change in fat-free mass at 8 weeks (kg) for sibutramine 10–20 mg/day versus placebo*

(–1.8 kg versus –0.2 kg, $p < 0.001$). There were no statistically significant between-group differences for change in fat-free mass or change in waist–hip ratio.[44]

The groups did not differ significantly in terms of patients requiring a change in the dose of anti-diabetic therapy during the trial. In terms of glycaemic control, fasting blood glucose levels decreased relative to baseline in the sibutramine group (0.3 mmol/l) and increased in the control group (1.4 mmol/l). Assessment after test meals were undertaken at baseline and at week 12. After the week 12 test meal, mean peak blood glucose level decreased by 1.1 mmol/l from baseline to endpoint in sibutramine-treated patients and increased by 0.5 mmol/l in patients given placebo ($p = 0.04$, mean difference –1.6: 95% CI, –3.3 to –0.1). Fasting insulin levels in patients not receiving exogenous insulin showed a median decrease at endpoint of 1.9 mU/l in the sibutramine group and a rise of 0.5 mU/l in the control group. Mean glycosolated haemoglobin decreased by 0.3% in those receiving sibutramine but did not change in the control group. A total of 15 out of 45 (33%) sibutramine-treated patients experienced a decrease in glycosolated haemoglobin levels of ≥ 1% at endpoint compared with 2/41 (5%) of control patients ($p < 0.05$). A greater decrease in glycosolated haemoglobin was associated with a greater reduction in weight in patients receiving sibutramine.[44]

Adverse events and withdrawals

No significant differences were found between groups for changes in BP; however, sibutramine-treated patients showed a significantly greater increase in radial pulse rate (7.5 bpm (beats per minute) versus 0.2 bpm; $p = 0.005$). ECG heart rate changes were consistent with pulse rate changes. No clinically significant conduction or rhythm abnormalities were observed on ECG.[44]

Adverse events were reported by 45/47 (96%) of patients given placebo and 42/44 (95%) of sibutramine-treated patients, and were reported as mild or moderate in severity for most patients. The trial authors considered that 7% of adverse events in the sibutramine group and 1% in the placebo group were associated with the treatment. The most common adverse events reported were headache, constipation, dry mouth, infection, pharyngitis and dizziness. Two patients receiving placebo withdrew due to adverse events (one for giddiness and vomiting, one for headache), and three withdrew from the sibutramine group (one each for dizziness, insomnia and diarrhoea).[44]

Hanotin et al., *1998*[45]

A multicentre trial involved an alternative active drug as comparator for sibutramine, namely the centrally acting appetite suppressant dexfenfluramine.[45] It should be noted that fenfluramine and dexfenfluramine have now been withdrawn from use due to a possible association between valvular heart disease and the use of these drugs.[32] Patients aged 18–65 years with a BMI of at least 27 kg/m^2 were included; those with type-1 or type-2 diabetes were excluded. The authors state that all participants received dietary therapy and behavioural modification advice given in accordance with the usual practice of the investigators, but no further details of this were provided in the paper. Patients were randomised to receive sibutramine 10 mg/day or dexfenfluramine 30 mg/day. A 1–2-week run-in period took place prior to randomisation, and was for screening purposes only.[45]

The study authors presented the results in terms of central estimates with 90% CIs. ITT analyses of change in body weight showed a greater mean reduction in the sibutramine group compared with dexfenfluramine (–4.5 kg versus –3.2 kg; 90% CI of the difference between means, –2.1 to –0.5). A similar pattern of results was seen for analysis of completers, and also for analyses of percentage body weight lost. In all, 46% of patients in the sibutramine group and 34% in the dexfenfluramine group lost more than 5% of initial body weight, analysed by ITT. The figures for completers were 48% and 38%, respectively. Secondary analyses involved comparing the two drugs with reference to a predetermined equivalence range of –2 kg to +2 kg. This meant that one treatment was considered to be superior to the other by a value exceeding 2 kg, a value decided by consensus. ITT analysis of weight loss indicated significantly superior performance of sibutramine versus dexfenfluramine. Both groups experienced reductions in mean waist and hip measurements, but there were no statistically significant between-group differences. Likewise, there was no between-group difference for change in waist–hip ratio. Both groups experienced reductions in plasma triglycerides and total cholesterol concentration.[45]

This trial also reported weight maintenance at 4 weeks following discontinuation of the 12-week weight loss intervention. No details were given of whether the diet alone (i.e. without medication) was continued during this time, or whether specific measures were taken to maintain weight loss. Four weeks after discontinuation of therapy, the two groups were comparable for weight change (95% CI for the between-group difference, –0.7 to 0.2), with a mean ± SD of 0.5 ± 1.6 kg for the sibutramine group and 0.8 ± 1.6 kg for the dexfenfluramine group.[45]

Adverse events and withdrawals

Both groups experienced small increases in mean SBP at 12 weeks. For DBP, the dexfenfluramine group showed a small decrease in mean value (–1.1 mmHg) and the sibutramine group had a small increase (+0.4 mmHg). For mean change in pulse rate, the dexfenfluramine group showed a small decrease (–0.9 bpm) and the sibutramine group experienced a small increase (+3.6 bpm). The mean heart rate measured from ECG was comparable with mean pulse rate. No other clinically significant ECG changes were noted.[45]

A total of 90 patients in the dexfenfluramine group reported 250 adverse events, and 84 patients in the sibutramine group reported 233 adverse events. There were 11 withdrawals due to adverse events in the dexfenfluramine group and six in the sibutramine group. The reasons for withdrawal in the dexfenfluramine group included articular pain, asthenia, dizziness, epigastralgia, facial erythema/conjunctivitis, headache, hypotension/nervousness, sciatica, traumatic vertebral fracture and nausea/vomiting/vertigo. The reasons for withdrawal in the sibutramine group included abdominal pain, allergic urticaria, depression, headache/thoracic pain, migraine and nausea/dizziness. Articular pain, sciatica, vertebral fracture and depression were described by the trial authors as "serious adverse effects not considered to be related to study therapy".[45]

The most commonly reported adverse events in both groups were constipation, flu syndrome, dry mouth, headache, asthenia, abdominal pain, insomnia, nausea, pharyngitis, infection and diarrhoea. Asthenia, abdominal pain, insomnia, infection and diarrhoea occurred more frequently in the dexfenfluramine group. Constipation, flu syndrome, dry mouth and headache occurred more frequently in the sibutramine group. Similar numbers of patients from both groups reported nausea and pharyngitis.[45]

Walsh et al., *1999*[43]

In a third, very small trial (n = 19), female patients aged 18–65 years with a BMI within the range 30–44 kg/m^2 were recruited. All patients were instructed to follow a calorie-reduced diet, with an energy deficit of 600 kcal/day, and were randomised to receive either sibutramine 15 mg/day or placebo for 12 weeks.[43]

All outcomes were assessed in terms of percentage change. There were no statistically significant differences between groups for percentage change in body weight, fat mass, fat-free mass, waist circumference, hip circumference, waist–hip ratio, fasting insulin or insulin–glucose ratio. However, the between-group difference for change in body fat mass was statistically significant in favour of sibutramine (–14.2% versus –6.3%, p = 0.04). It is possible that this small trial lacked the statistical power to detect true treatment effects for some outcomes. No significant adverse events were reported in either group.[43]

Consideration of pooled analyses at 12-week endpoint

Two trials reported percentage change in body weight,[43,45] but variance was not reported for one,[45] and therefore they could not be pooled.

Two trials reported change in body weight and patients achieving more than 5% loss of initial weight.[44,45] These were not pooled due to differences in participant and comparator intervention characteristics. In one trial, only people with type-2 diabetes were recruited,[44] and in the other the appetite suppressant dexfenfluramine was the comparator intervention for sibutramine, as opposed to placebo.[45] It was not considered appropriate to pool trials with such differing characteristics.

RCTs with a 6-month endpoint

Four trials reported results at a 6-month endpoint.[41,42,47,48] The effects of sibutramine 10 mg/day,[42] 15 mg/day[48] and dose titration from 5 mg up to 20 mg/day,[47] all versus placebo, were examined. The other trial was a dose ranging study.[41]

Fanghanel et al., *2000*[42]

In the first study, patients aged 16–65 years with a BMI greater than 30 kg/m^2 were recruited. People with type-2 diabetes were not excluded. All patients were asked to consume a diet based on 30 kcal/kg of ideal body weight/day, containing 50% of calories as carbohydrates, 30% as fats and 20% as proteins. Patients received this advice 15 days prior to being randomised to either sibutramine 10 mg/day or placebo for 6 months.[42]

The mean weight change in the sibutramine group was –8.61 kg compared with –4.03 kg in the placebo group. The respective mean values for percentage of baseline weight remaining at 6 months were 90.11% and 95.23%, and for mean change in BMI were –3.59 kg/m^2 and –1.66 kg/m^2. The mean change in waist circumference in the sibutramine group was –8.09 cm compared with –4.69 cm in the placebo group; respective changes in the waist–hip ratio were –0.021 and –0.028. All analyses were by ITT. It was unclear whether the between-group differences were statistically significant. In all, 85% of sibutramine-treated patients achieved greater than 5% loss of body weight relative to baseline compared with 48% of patients given placebo. The figures for 10% loss of initial weight were 45% and 9% respectively.[42]

In sibutramine-treated patients, appetite reduced significantly from the first month through to the end of the trial, and these patients also had increased satiety in the first 3 months as well as better adherence to the diet during the first month. Patients in the placebo group had significantly less appetite during the first and fifth months of treatment and did not have any significant changes in satiety or diet adherence. Appetite, satiety and adherence to the diet were assessed using the VAS.[42]

Adverse events and withdrawals

No treatment-related adverse events were noted in terms of changes in BP. ECG assessments did not show any significant changes in the sibutramine group, but patients in the placebo group showed small, statistically significant fluctuations in heart rate and ST segment ($p < 0.05$).[42]

Adverse events reported by both groups included dry mouth, statistically significant increases in BP and heart rate, urinary tract infection, headache and hypersomnia. Constipation and insomnia only occurred in the sibutramine group. Dry mouth, significant increase in heart rate, constipation and insomnia were reported more frequently in the sibutramine group. Significant increases in BP occurred more often in the placebo group. Urinary tract infection, headache and hypersomnia occurred in small and roughly equal numbers in both groups. Most of the adverse effects in sibutramine-treated patients occurred during the first 2 months of treatment. Two patients in the sibutramine group and one in the placebo group left the trial due to adverse events.[42]

Cuellar et al., *2000*[48]

In the second trial, patients aged 16–65 years with a BMI greater than 30 kg/m^2 were recruited. People with type-2 diabetes were not excluded. There was no run-in period. All patients were instructed to consume a diet based on 30 kcal/kg ideal body weight/day and received printed information and brief dietary counselling. They were randomised to receive either sibutramine 15 mg/day or placebo for 6 months, with approximately 35 participants allocated to each treatment group.[48]

This trial used an unusual definition of analysis by ITT, basing this on participants who had completed the trial. The following data are based on last observation carried forward (LOCF) analysis at 6 months. The mean weight change at 6 months was –1.3 kg in the placebo group and –10.4 kg for the sibutramine group; mean changes in BMI were –0.5 kg/m^2 and –4.2 kg/m^2, respectively; mean changes in waist circumference were –3.3 cm and –12.5 cm, respectively; and mean changes in waist–hip ratio were –0.01 and –0.04, respectively. The analysis of variance (ANOVA) (based on completers' data) for multiple measures of the above variables showed the interaction of the effect of time with medication as statistically significant ($p < 0.001$ for the first three measure-

ments; $p < 0.022$ for waist–hip ratio). Similar results were seen for LOCF ANOVA. The proportions of patients losing 5% of initial body weight were 9.7% in the placebo group and 76.5% in the sibutramine group. For 10% loss, the figures were zero and 55.9%, respectively. The difference in the cumulative incidence of both 5% and 10% loss of initial weight was statistically significant ($p < 0.001$).[48]

Sibutramine-treated patients had more favourable scores than patients given placebo throughout the trial for decreased appetite, increased satiety and better adherence with the diet. These outcomes were assessed using a VAS.[48]

Adverse events and withdrawals

No statistically significant between-group differences were observed for SBP, DBP, heart rate or ECG at 6 months. Overall, 23 sibutramine-treated patients reported 34 adverse events and 16 patients given placebo reported 21 adverse events. The numbers per group for each type of adverse event were small. Three patients in the sibutramine group compared to none in the placebo group withdrew due to adverse events. A total of 17 and seven respectively withdrew due to lack of efficacy.[48]

Fujioka et al., *2000*[47]

For the dose-titration study, patients aged at least 18 years with a BMI 27–40 kg/m^2 were recruited. In addition, eligible patients had a diagnosis of type-2 diabetes, treated with either diet alone or diet plus a single oral anti-diabetic agent (a sulphonylurea or metformin). All patients underwent a 5-week, single-blind, placebo run-in period when they received dietary counselling and a nutrition plan designed to achieve a minimum energy deficit of 250–500 kcal/day. Patients achieving a fasting plasma glucose (FPG) level within the range 7.8–12.8 mmol/l and glycosolated haemoglobin of greater than 7% during the run-in were eligible to enter the double-blind treatment phase. The dietary regimen commenced during the run-in period continued throughout the trial, and patients were randomised to receive either sibutramine or placebo. The initial dose of sibutramine was 5 mg/day, titrated up to 20 mg/day by 5 mg increments every 2 weeks until week 6. The 20 mg/day dose was then continued until the end of the trial (week 24).[47]

Data reported here are based on LOCF analysis at 24 weeks. The mean weight change was –0.4 kg in the placebo group and –3.7 kg in the sibutramine group ($p \leq 0.05$). The between-group difference remained at the same level of statistical significance for each subgroup when analysis was undertaken according to the method of treating diabetes: diet alone, diet plus sulphonylurea or diet plus metformin. The mean change in BMI was –0.2 kg/m^2 in the placebo group and –1.3 kg/m^2 in the sibutramine group ($p < 0.001$). The proportions of patients achieving 5% loss of initial weight were 1.2% in the placebo group and 27% in the sibutramine group ($p < 0.001$). The respective figures for 10% loss of initial weight were 1.2% and 6%, and were not significantly different.[47]

The mean change in hip circumference was –0.7 cm for patients given placebo and –3.0 cm for sibutramine-treated patients ($p = 0.01$). The between-group difference in mean waist circumference was not statistically significant. It was unclear whether these analyses were based on LOCF or completers.[47]

In terms of glycaemic control, improvement in FPG level and glycosolated haemoglobin concentration was significantly and positively correlated with percentage change in body weight in sibutramine-treated patients ($p = 0.0064$ and $p = 0.001$, respectively), but not in patients given placebo. Based on LOCF analyses at 24 weeks, between-group differences for glycosolated haemoglobin concentration and FPG levels were not statistically significant. However, sibutramine-treated patients achieved a significantly greater reduction in fasting plasma insulin relative to placebo (reduction of 11.0 pmol/l versus increase of 1.0 pmol/l; $p \leq 0.05$).[47]

Sibutramine-treated patients achieved significantly larger mean decreases in triglycerides versus patients given placebo ($p = 0.004$). However, the between-group difference in change in high-density lipoprotein cholesterol (HDL-C) level was not statistically significant.[47]

In terms of QoL assessments, scores from sibutramine-treated patients indicated more favourable changes relative to those seen in patients given placebo for both the generic Medical Outcome Study 36-item short form health survey (SF-36)[57] and the more condition-specific 74-item Impact of Weight on Quality of Life questionnaire.[58]

Adverse events and withdrawals

Changes in supine and postural SBP and DBP and in postural pulse rate did not differ significantly between groups. However, sibutramine-treated patients showed a modest but statistically significant increase in pulse rate compared with patients

given placebo: 4.0 bpm (placebo); 5.9 bpm (sibutramine) ($p < 0.001$, LOCF). In the placebo group, 275 adverse events were reported by 68 patients and in the sibutramine group 250 adverse events were reported by 70 patients. Adverse events that were classified as 'serious' occurred in one patient given placebo and five sibutramine-treated patients. The authors of the trial considered that the relationship to study drug was possible in only one of the sibutramine-treated patients. Overall, 25 out of 86 (29%) of patients given placebo and 29 out of 89 (33%) of sibutramine-treated patients withdrew during the double-blind trial. Of these, ten and nine patients respectively withdrew due to adverse events.[47]

Bray et al., *1999*[41]

For the dose-ranging trial, patients aged 18–65 years with a BMI of 30–40 kg/m^2 were included. All patients underwent a 2-week placebo run-in period and received nutritional counselling. During the double-blind trial, female patients were instructed to consume 1200 kcal/day, and male patients 1500 kcal/day. An exercise programme consisting of walking for 20–30 minutes/day was advised, and all were instructed in behavioural change techniques. Participants were randomly allocated to receive placebo or sibutramine for 24 weeks at one of the following daily doses: 30 mg, 20 mg, 15 mg, 10 mg, 5 mg or 1 mg.[41]

All changes were assessed relative to baseline values. Analysis of those completing the trial showed that weight loss, assessed as a percentage of baseline weight, was dose-related and statistically significant versus placebo across all time points for the sibutramine 30 mg, 20 mg, 15 mg, 10 mg and 5 mg groups ($p < 0.05$). It is not stated whether the between-group differences were statistically significant for percentage weight loss (ITT) or absolute weight loss (kg) (completers). For the analysis of patients losing at least 5% of baseline weight at 24 weeks, differences were statistically significant between placebo and sibutramine groups at sibutramine doses of 30 mg, 20 mg, 15 mg, 10 mg and 5 mg ($p < 0.01$). A similar pattern of results, with similar observation of statistically significant between-group differences, was seen for those losing at least 10% of initial weight.[41]

Adverse events and withdrawals

The following adverse events prompted dose reductions: asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash and dyspnoea. The rate of withdrawals due to adverse events did not appear to be dose related. Patients in some sibutramine groups (10 mg, 15 mg, 20 mg, 30 mg) experienced significantly increased pulse rate relative to placebo ($p < 0.05$), and patients in the sibutramine 20 mg/day group experienced significantly raised DBP compared to placebo ($p < 0.05$).[41]

Pooled analyses for 6-month endpoint

Two trials evaluating sibutramine 10 mg/day versus placebo were pooled to give a summary RR (random-effects model) of failure to achieve at least 5% loss of initial body weight of 0.48 (95% CI, 0.39 to 0.60, $p < 0.00001$; test for heterogeneity chi-squared = 0.22, df = 1, $p = 0.64$; *Figure 4*).[41,42]

However, significant heterogeneity was observed when trials were pooled for the same outcome at the 15 mg dose[41,48] and for the risk of failing to achieve at least 10% of initial weight loss for sibutramine 10 mg/day[41,42] and 15 mg/day.[41,48]

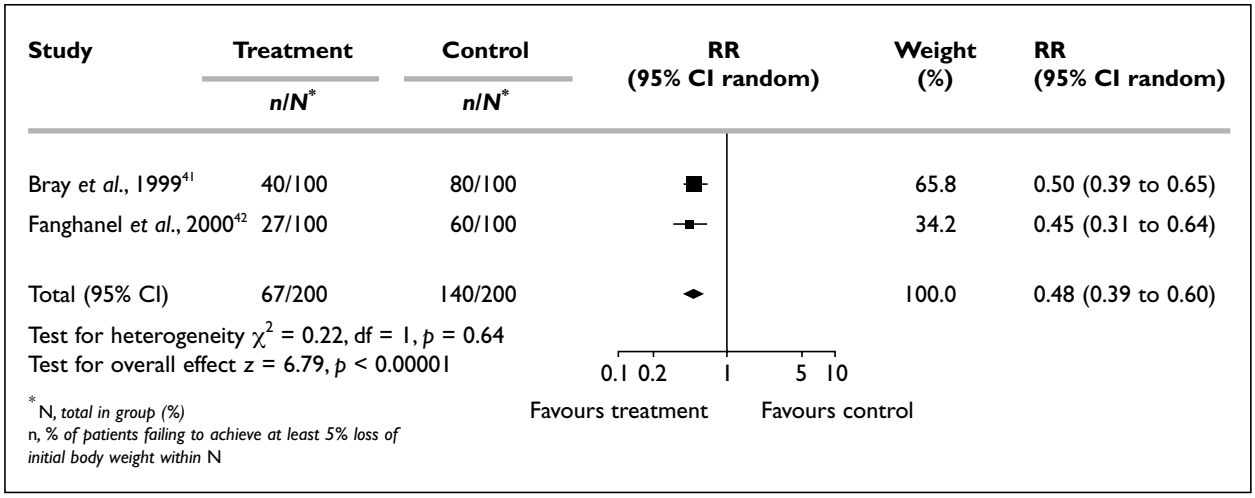

FIGURE 4 *Relative risk of failure to achieve at least 5% loss of initial body weight for sibutramine 10 mg/day versus placebo*

RCTs focusing on weight maintenance

Weight maintenance is considered to involve a different treatment goal to weight loss, and has therefore been considered separately. Two trials included components of weight maintenance in addition to weight loss programmes, and have already been discussed.[39,45]

Apfelbaum et al., *1999*[46]

One trial focused on weight maintenance following a brief weight loss intervention.[46] Patients aged between 18 and 55 years with a BMI greater than 30 kg/m^2 were recruited. Initially, a 1-week run-in period was undertaken by all patients, and this was for screening purposes only. All patients then underwent a 4-week very-low-calorie diet (VLCD) for weight loss, with an energy intake of 220–800 kcal/day. At the end of this time, patients achieving a weight loss of at least 6 kg were eligible to enter the double-blind maintenance phase and were randomised to receive either sibutramine 10 mg or placebo for 12 months. During the maintenance period, the VLCD was discontinued and patients resumed normal meals and received dietary counselling to decrease their total calorie intake by 20–30% relative to their consumption prior to the VLCD.[46]

The mean values for weight change at 12 months relative to weight at randomisation were –5.2 kg for the sibutramine group and +0.5 kg for the placebo group ($p = 0.004$). Proportions of patients maintaining at least 5% loss of baseline weight at 12 months were 86% for sibutramine and 55% for placebo ($p < 0.001$). The respective figures for at least 10% loss were 54% and 23% ($p < 0.001$), and for 20% loss or more were 17% and 3% ($p < 0.01$). A total of 96% of patients in the sibutramine group and 83% in the placebo group maintained 25% or more of their weight loss at 12 months ($p < 0.01$). The respective figures for those maintaining 50% loss or more were 93% and 76% ($p < 0.01$), and for 100% loss or more were 74% and 41% ($p < 0.001$). The mean changes in waist circumference at 12 months were –6 cm for sibutramine and –1 cm for placebo ($p < 0.001$).[46]

After 12 months, the drugs were discontinued. Then, 3 months later weight regain was assessed and was significantly different between groups: 4.3 kg for sibutramine and 2.3 kg for placebo ($p = 0.009$).

From baseline to 12 months, triglyceride levels were reduced and high-density lipoprotein cholesterol (HDL-C) levels were increased in the sibutramine group in comparison with the placebo group ($p < 0.05$). No other between-group differences in lipid levels were noted. LDL-C levels increased in both groups from baseline levels when patients received the VLCD.[46]

Adverse events and withdrawals

There were no statistically significant changes between groups for change in SBP; however, there was a significant between-group difference for the change from baseline in DBP (–1.9 mmHg for placebo, +1.5 mmHg for sibutramine; $p < 0.05$). Pulse rate increased significantly at all time points in the sibutramine group compared with placebo ($p < 0.05$). Heart rate (measured from ECG) increased in both groups. The mean difference between placebo (+1 bpm) and sibutramine (+8 bpm) was statistically significant at 6 months only ($p < 0.001$). No other clinically important ECG changes were observed.[46]

A total of 72 patients (88%) in the sibutramine group reported 331 adverse events and 63 patients (81%) patients in the placebo group reported 309 adverse events. The most commonly reported adverse events included pharyngitis, constipation, headache, bronchitis, back pain, anxiety, asthenia, flu syndrome, insomnia, nausea and dry mouth. Constipation, headache, bronchitis, back pain, anxiety, insomnia, nausea and dry mouth all occurred more often in the sibutramine group. The frequency of constipation was statistically greater in the sibutramine group (15 patients reporting constipation versus four patients; $p = 0.01$). Pharyngitis, asthenia and flu syndrome occurred in approximately equal numbers in both groups. There were five withdrawals due to adverse events in the placebo group (two pregnancies, one for chest tightness, one for development of hypertension and one for headache, insomnia and dizziness) and two in the sibutramine group (one anxiety and one depression).[46]

RCTs from the company submission

A further five trials on sibutramine that were submitted by the drug company were included in the review.[49–53]

Wirth, 1998[49]

In the first trial,[49] patients with a BMI of 30–40 kg/m^2 were recruited to undergo a 4-week, open label treatment period with sibutramine 15 mg/day. Those losing at least 2 kg or at least 2% of initial body weight were eligible to enter the double-blind trial. During the double-blind treatment period, patients were given general dietary advice concerning healthy eating and

calorie reduction. Patients were randomised to receive one of the following: sibutramine 15 mg/day continuously for 48 weeks (n = 405) (I2); sibutramine 15 mg/day given intermittently in 12-week blocks during a 48-week period, separated by 6-week intervals on placebo (n = 395) (I1); or sibutramine 15 mg/day for 4 weeks followed by placebo for 44 weeks (n = 201) (C).

Although three treatment groups were included in the trial, results based on ITT analyses were only reported for group I2 (continuous sibutramine) and group C (sibutramine/placebo). At 1 year, the mean weight change was –7.9 kg and –3.8 kg, respectively. Greater proportions of patients in group I2 lost 5% and 10% of baseline body weight compared with group C (65% versus 35% for 5% loss, and 32% versus 13% for 10% loss, respectively). None of these data were accompanied by tests of statistical significance, and variance around the central estimates was not reported.

Adverse events and withdrawals

Very few data were provided on adverse events and withdrawals.[49]

Smith, 1994[50]

In a second trial,[50] patients with a BMI of 27–40 kg/m^2 were recruited. All underwent a 2-week washout period. Dietary advice (not specified) was given before the washout and throughout the study. Patients were randomised to receive either sibutramine 15 mg/day (n = 161), sibutramine 10 mg/day (n = 161) or placebo (n = 163) for 1 year.

Mean weight change based on LOCF was –6.4 kg for 15 mg, –4.4 kg for 10 mg and –1.6 kg for placebo ($p < 0.01$ for 10 mg versus placebo, and $p < 0.001$ for 15 mg versus placebo). Sibutramine-treated patients were significantly more successful than patients receiving placebo at losing more than 5% or 10% of baseline body weight. Based on completers' data, the figures for those losing more than 5% baseline weight were 65% for 15 mg, 56% for 10 mg and 29% for placebo ($p < 0.01$ for 10 mg versus placebo, and $p < 0.001$ for 15 mg versus placebo). The respective values for 10% loss were 39%, 30% and 8% ($p < 0.01$ for 10 mg versus placebo, and $p < 0.001$ for 15 mg versus placebo).[50]

Adverse events and withdrawals

The following numbers of patients withdrew due to adverse events: sibutramine 15 mg group, 20 patients; 10 mg group, 18 patients; placebo group, 24 patients. Respective numbers of patients withdrawing due to lack of efficacy were two, five and ten.

This trial has been published since completion of this report.[55] The information described in this report is based on details provided by the manufacturer at the time that the review was being prepared.

James, 1999[51]

In the third trial,[51] patients aged between 18 and 65 years with a BMI of 30–45 kg/m^2 were recruited to undergo a 6-month run-in period when all received sibutramine 10 mg/day throughout. Data at baseline were not reported. Exact numbers for change in body weight were not provided (shown on figure only). Patients losing at least 5% of their baseline body weight were eligible to enter the double-blind phase of the study. During the double-blind phase patients followed a reduced calorie diet with an energy deficit of 600 kcal/day in combination with an exercise plan based on each patient's basal metabolic rate, measured at screening, month 3 and month 6. Patients were randomised to receive one of the following weight maintenance regimens: sibutramine with dose titrated according to weight change (10 mg, 15 mg or 20 mg daily) (n = 352) or placebo (n = 115).

At study endpoint (18 months from start of double-blind treatment), 41% of sibutramine-treated patients had successfully maintained their weight loss compared with 14% in the placebo group ($p < 0.001$). The mean weight change from baseline to endpoint was –8.9 kg and –4.9 kg, respectively ($p < 0.001$).

Adverse events and withdrawals

A total of 48 sibutramine-treated patients and six patients receiving placebo withdrew due to adverse events.[51]

This trial has been published since completion of this report.[56] The information described in this report is based on details provided by the manufacturer at the time that the review was being prepared.

Rissanen, 1998[52]

In the fourth trial,[52] obese patients with type-2 diabetes who had never received anti-diabetic medication were recruited. All underwent a 2-week placebo run-in period and commenced a reduced calorie diet with an energy deficit of 700 kcal/day. The dietary regimen continued throughout the double-blind phase of the study, when patients

were randomised to receive sibutramine 15 mg/day (n = 114) or placebo (n = 122).

Results based on ITT analyses were in favour of sibutramine at month 12. The mean weight change was –7.5 kg in the sibutramine-treated group and –2.7 kg in the group given placebo ($p < 0.001$). The mean changes in BMI were –2.7 kg/m^2 and –0.9 kg/m^2 respectively ($p < 0.001$). In addition, better results were seen for changes in waist and hip circumferences and waist–hip ratio for sibutramine-treated patients compared to placebo. The mean change in waist circumference was –7.1 cm for sibutramine-treated patients and –3.3 cm for those receiving placebo ($p < 0.001$). The mean changes in hip circumference were –4.7 cm and +1.9 cm respectively ($p < 0.001$), and for waist–hip ratio × 100 were –2.5 and –1.3 ($p < 0.05$), respectively. In terms of glycaemic control, there were no statistically significant between-group differences for glycosolated haemoglobin concentration or fasting glucose. There were statistically significant larger reductions in the sibutramine group relative to placebo for triglycerides ($p < 0.001$) and larger increases in HDL-C ($p < 0.001$), but no significant between-group differences were observed for levels of total cholesterol or LDL-C.[52]

Adverse events and withdrawals

Nine sibutramine-treated patients and 12 patients given placebo withdrew due to adverse events.[52]

Williams, 1999[53]

In the fifth trial,[53] obese patients with type-2 diabetes, stabilised with metformin, were recruited. All patients were given general dietary advice and were randomised to receive either sibutramine 20 mg/day (n = 62), sibutramine 15 mg/day (n = 69) or placebo (n = 64) for 1 year.

ITT analyses showed favourable results for the sibutramine groups compared with placebo at 1 year. The values for mean weight change were –8.5 kg for the sibutramine 20 mg group, –6.2 kg for the 15 mg group and –0.2 kg for placebo ($p < 0.001$ for both sibutramine groups versus placebo). Similar results were seen for change in BMI (–3.2 kg/m^2, –2.2 kg/m^2 and –0.1 kg/m^2, respectively; $p < 0.001$ for both sibutramine groups versus placebo). Statistically significant results in favour of sibutramine were also seen for change in waist and hip circumferences at 12 months; however, the between-group difference for the waist–hip ratio was not statistically significant. No statistically significant between-group differences were observed for change in glycosolated haemoglobin concentration, FPG levels and fasting plasma insulin levels at 1 year. Likewise, no statistically significant between-group differences were observed for lipid level parameters.[53]

Adverse events and withdrawals

A total of 11 patients in the sibutramine 15 mg group, three from the 20 mg group and five patients from the placebo group withdrew due to adverse events.

Economic evaluations

Appendix 5 shows a data extraction table and appendix 6 summarises the quality assessment.

No published economic evaluations were identified. The manufacturer submitted a cost– utility analysis of sibutramine in the treatment of obesity.[54]

The main model was based on data from two placebo-controlled trials where the drug regimen was combined with a dietary and exercise programme.[50,51]

The first trial started with a 6-month run-in period in which all patients received sibutramine 10 mg once-daily. This was followed by an 18-month placebo-controlled double-blind phase when all patients received a 600 kcal/day deficit diet and an exercise plan. Those in the sibutramine group received 10 mg, 15 mg or 20 mg, with the dose titrated according to weight change.[51] The second trial started with a 2-week wash-out period for all patients (dietary advice was given at the outset), followed by a 12-month placebo-controlled double-blind phase. During this time all patients were provided with dietary advice and those in the two active drug arms received sibutramine 10 mg/day or 15 mg/day.[50]

The patient group employed in the economic model had a BMI > 30 kg/m^2 and were free of co-morbidities and complications at the start of the modelling period (n = 1000). The model was built around three elements:

- the effect of sibutramine-induced weight loss on CHD risk
- the effect of sibutramine-induced weight loss on the incidence of diabetes
- the direct effect of sibutramine-induced weight loss on QoL.

The cost-effectiveness of sibutramine in each element was estimated separately, calculating the

cost per quality-adjusted life-year (QALY) gained. It was assumed that no patient would maintain any weight loss at 5 years. Costs were discounted at 6% and benefits at 1.5% following Treasury recommendations.

The results were as follows:

- The QoL coefficient for sibutramine was 0.00185/kg lost (95% CI, 0.00048 to 0.00322) and for placebo 0.00142 (95% CI, 0.00058 to 0.00341).
- The cost per QALY gained through CHD reduction alone was £42,000, and through diabetes incidence reduction alone £77,000.
- Utility results combined with weight loss and weight regain evidence from trials produced an estimated cost per QALY from weight loss alone of £19,000. This resulted in a combined cost per QALY of £10,500.

The model was tested for its sensitivity to the following variables: slope of regain curve, utility/kg lost, monitoring costs after 12 months, monitoring costs for drop-outs, prescribing costs of diabetes, inclusion of effects on CHD during years 2–5, inclusion of effects on diabetes during years 2–5, diabetes QALY multiplier and drug price.

Outcomes of the sensitivity analysis ranged from £3200 (monitoring costs incurred by the placebo group after 2 years) to £16,700 (lower utility gained/kg lost). The single worst case scenario resulted in £35,200 per QALY gained and the single best case scenario resulted in £5700 per QALY gained.

QALY scores for the sample population were adjusted from higher initial scores than those found in a survey of the general population.[59] The validity of the results is highly dependent on QALY estimates and the methods used to derive them. The authors do not explain why the starting utility of the obese cohort was significantly higher than the age-related utility data from the study cited above, which was based on a survey of the general population (n = 3381).[59] This has considerable implications for the cost per QALY. A sensitivity analysis was carried out with lower utility gains per kg (0.00048 for sibutramine and 0.00058 for placebo), which resulted in a cost per QALY of £50,400.

Chapter 4

Discussion and conclusions

Note that, where possible, the mean difference between treatment and control groups is shown in terms of ITT analyses, and relates to a 10–20 mg/day dose of sibutramine.

Clinical effectiveness

Results from most individual trials and pooled estimates suggested that sibutramine, administered at daily doses of 5–30 mg, produced greater weight loss compared with placebo (statistically significant) at all observed endpoints.[38–41,48] For daily sibutramine doses of 10–20 mg prescribed to non-diabetic participants, the WMD for weight change in favour of the active drug at 8 weeks was –3.4 kg,[38–40] and the mean difference range from trials with a 6-month endpoint was from –4.0 to –9.1 kg[41,42,48] and from –4.1 to –4.8 kg at 1 year.[49,50] Findings from dose-ranging studies suggested a dose–effect relationship in terms of weight loss.[40,41] Results from mainly small trials showed that sibutramine produces more favourable outcomes in terms of loss of fat mass at 8 weeks,[38,39] reduction in BMI at 8 weeks and 6 months,[39,48] greater proportions of patients losing at least 5% of initial body weight at 8 weeks and 6 months[39,41,48] and 10% loss at 8 weeks and 6 months.[39,41,48] In addition, sibutramine decreased the sensation of hunger[38,39,42,48] and increased satiety compared with placebo.[38,42,48]

Between-group differences for cardiovascular risk indicators such as waist circumference, hip circumference and waist–hip ratio did not reach statistical significance in most trials assessing these outcomes.[39,43,44,47] The statistical significance of between-group differences was unclear in one trial in terms of weight loss and change in BMI, waist circumference and waist–hip ratio.[42] One very small trial did not show statistically significant differences between groups for any outcome.[43]

There were four trials for which only patients with type-2 diabetes were recruited.[44,47,52,53] One small trial showed that sibutramine achieved statistically significantly better weight loss (mean difference 2.3 kg at 12 weeks), decreased BMI, reduced fat mass and had more patients losing at least 5% of initial body weight at 12 weeks compared with placebo.[44] However, there were no statistically significant between-group differences for change in waist–hip ratio, and findings in terms of changes in glycaemic control did not show consistent statistically significant benefits of sibutramine use. Another trial, which had a 6-month endpoint, showed that sibutramine achieved statistically significant greater weight loss relative to placebo (mean difference 3.3 kg), change in BMI and the proportion of patients losing at least 5% of initial body weight.[47] However, statistically significant between-group differences were not seen in terms of loss of 10% of initial weight and changes in indicators of glycaemic control. In two trials with a 1-year endpoint, the mean difference range was 4.8–6.0 kg, statistically significant in favour of sibutramine.[52,53] However, between-group differences for changes in indicators of glycaemic control were not statistically significant.

Sibutramine performed more favourably than dexfenfluramine (now withdrawn) in producing weight loss (mean difference 1.5 kg at 12 weeks) and promoting greater than 5% loss of initial weight. However, there were no statistically significant between-group differences for changes in waist circumference, hip circumference and waist–hip ratio.[45]

In terms of weight maintenance, results from one trial showed that when sibutramine was compared with placebo as part of a 1-year weight maintenance regimen following a VLCD, use of the active drug achieved better results in terms of change in body weight (mean difference 5.7 kg after 1 year of double-blind treatment) and maintaining at least 5%, 10% and 20% of initial loss of body weight – all statistically significant. However, in absolute terms, sibutramine-treated patients experienced statistically significant greater regain 3 months after stopping treatment.[46] In a second trial, comprising 18 months double-blind treatment as a weight maintenance programme, the mean difference in favour of sibutramine was 4.0 kg.[51]

Adverse effects

Some trials showed that sibutramine use was associated with small but statistically significant increases in pulse rate, heart rate and BP. It is possible, however, that these changes were not

of clinical significance.[38,41,47,48] Results from a small trial suggested that sibutramine use may be associated with increased frequency of headache, sleep difficulty and irritability.[40]

Economic evaluations

One economic evaluation of sibutramine was identified,[54] giving a combined cost per QALY of £10,500. Sensitivity analysis produced an estimated range from £5700 (single best case scenario) to £35,200 (single worst case scenario).

Limitations of the trials

In general, the methodological quality of included trials was moderate or good. Relatively few trials reported the use of methods to produce true randomisation. However, all the trials were described as 'double-blind' and were placebo-controlled with one exception, which used an alternative anti-obesity drug (matched to the study medication) as a comparator.[45]

All included trials reported selection criteria for participants, reported group comparability at baseline and expressed an intention to provide identical treatment to participants, apart from the drugs under study. Relatively few described the use of an *a priori* power calculation to estimate required sample size, and it is possible that some small trials lacked sufficient statistical power to detect statistically significant between-group differences for some outcomes.[38–40,43,44,48]

In all trials, patients were blind by the use of identical placebo or an alternative active drug designed to match the experimental agent. It was less clear whether caregivers and outcome-assessors were also blind. In reality though, this is likely to be the case, since the trials all used double-blind procedures, and it is probable that provision of care and outcome assessment were carried out by the same staff. Owing to adverse events that can occur with the use of sibutramine, there is the possibility that patients and study personnel may be able to guess that the active drug is being administered and not the placebo. In one study, this was mentioned as being a potential problem.[42] It is possible that study results could be biased if blinding is no longer valid. None of the trials included methods to determine the success of blinding of patients, caregivers or outcome-assessors.

All trials described the statistical methods used for data analysis and most reported results in terms of a central value with associated variance. Around half of the trials described methods to deal with missing data and around half performed analyses based on ITT. Failure to use ITT analysis may cause bias brought about by non-random withdrawal of participants from the study.

Many of the trials included in this review that performed analysis by ITT employed the LOCF method. This method involves filling in missing values by using the last observed value for that case, and therefore assumes that the outcome remains constant at the last observed value after withdrawal. Some problems have been identified with the use of this approach. If patients continue to take prescribed anti-obesity medication after withdrawal, the LOCF is likely to underestimate the true treatment effect in those taking the active drug. If patients discontinue medication, and subsequently regain weight, the LOCF is likely to overestimate the true treatment effect.[60]

It has been suggested that analyses based on actual treatment received following withdrawal are of more value in explaining the biological effects of treatment. To this end, the multiple imputation model has been proposed, which involves analysis based on treatment actually received after withdrawal as opposed to those to which participants were originally assigned. This involves a sensitivity analysis incorporating imputations obtained for a range of alternative assumptions of dose after withdrawal. The range of assumptions include continuation on the same treatment as that immediately prior to withdrawal, reversion to control treatment after withdrawal and assignment to treatment group dose that is the closest to the actual recorded dose after withdrawal. Ideally, trials should incorporate follow-up of withdrawals in order to record information on dosage received. Future trialists may wish to consider using the multiple imputation model as an alternative to the LOCF method.[60]

Reporting numbers of withdrawals per group with reasons was variable across the trials. Several trials included an assessment of patient adherence with the trial regimen. However, this was usually based on counting returned capsules (drug regimen) or assessing food intake from patients' self-reported account (dietary regimen), and both methods are potentially unreliable.

Many of the trials included in this review comprise a single-blind placebo run-in period prior to

double-blind treatment. Opinions differ as to the optimal approaches to analysis in trials of this type. One view is that the inclusion of weight loss occurring during the run-in period together with that achieved during double-blind treatment can be misleading, as it is the outcomes relating to the double-blind period that are the most important.[61] However, another view is that the run-in period is an important part of treatment because many risk-factor improvements occur during this time, and it should therefore be viewed as part of the whole treatment package.[62] Improved reporting and clarity in trials, relating to whether statistical calculations take the start of the run-in period or the start of double-blind treatment as the starting point, would assist in the interpretation of results.[63] One solution could be to report outcomes occurring during run-in separately from those for the double-blind period (starting from randomisation). Additional analyses could integrate outcomes during run-in and double-blind phases.

Generalisability of results

Use of sibutramine in younger people

Since most of the trials included in this review stipulated a minimum participant age of 18 years, little information is available on the possible effects of sibutramine in children and adolescents. Childhood obesity is an area of concern in the UK and other developed societies but has been more difficult to define and classify compared with adult obesity.[5,26] However, a definition of overweight and obesity in children, based on pooled international data for BMI and linked to the adult obesity cut-off point of 30 kg/m^2, has recently been proposed.[64] Despite this progress, options to prevent and treat obesity in younger people remain relatively limited. The WHO recommends that interventions in obese children should be designed to prevent weight gain rather than produce weight loss.[26] Another report emphasises the importance of a structured and multidisciplinary approach in this age group.[65] A previous systematic review found that family therapy and strategies to reduce sedentary behaviour may be promising interventions.[66] The issue of whether to use pharmacotherapy in childhood obesity is contentious. The Royal College of Physicians does not recommend the use of anti-obesity drugs in children due to lack of data about adverse effects on growth, development and future eating behaviour.[31] Another source reflects the same concerns, but explains that further research may help to identify subgroups of younger people who may benefit from combining pharmacotherapy with dietary and physical activity modification.[67] It is possible that investigation of the effectiveness and safety of sibutramine in younger people would be useful.

Use of sibutramine in older people

Most of the trials included in this review recruited patients under 65 years of age, reflecting a lack of information on the effectiveness and safety of sibutramine in older people. Despite the paucity of research in this age group, obesity is an important health problem in older age. In 1998, it was estimated that 48% of men in England aged 75 years and over were overweight and 16% were obese. The respective figures for women in the same age group were 37% and 20%.[4]

Two articles have highlighted pertinent issues around the use of pharmacotherapy in older people.[68,69] Aspects to be taken into account when prescribing include impaired gastric absorption and motility, and the effects of altered body composition on drug distribution. As the individual ages, fat mass increases whilst fat-free mass reduces. These changes affect the absorption of drugs according to whether they are lipophilic (fat-soluble) or hydrophilic (water-soluble). The higher proportion of fat mass present in older people means that lipophilic drugs will have a higher distribution volume. In the case of hydrophilic drugs, although there is a smaller volume of distribution, the concentration achieved may be higher. Both of these phenomena can cause problems with drug toxicity, meaning that the prescription regimen may need to be adjusted. In addition, impaired renal and hepatic function and the high likelihood of concurrent morbidities and use of polypharmacy, producing the possibility of drug interactions, need to be considered when planning pharmacotherapy in older people.[68,69] It is suggested that appropriate adjustment of drug regimens in older people can be achieved, but that attention should be paid to careful selection, dosing and monitoring in this age group. It is important that clinically significant effects, as distinct from those observed under controlled conditions, should be recognised.[69]

The findings of one pharmacokinetic study of sibutramine suggested that metabolism of the drug was similar in young (mean age 24 years) and elderly (mean age 70 years) healthy patients, and that a similar dosing regimen would be appropriate for both groups.[70] However, this was a small study (n = 24) which assessed

pharmacokinetics up to 48 hours following a single 15 mg dose of sibutramine. It should be noted that other pharmacokinetic studies are likely to be available, some of which may provide more detailed and useful information. However, it was not within the remit of this report to provide a full review of such studies.

Although evidence exists to suggest that weight loss is beneficial to health,[20] a debate exists as to the usefulness and appropriateness of pharmacotherapy in obese elderly patients. One view is that weight loss in older people who are relatively fit and independent should not be encouraged. This is because weight loss leads to loss of fat-free mass as well as loss of fat mass, and this could contribute to lower levels of muscular strength and functional independence.[68]

Given the lack of research in this age group, and the fact that the elderly population in developed societies is increasing, further research on the clinical effectiveness and safety of sibutramine in this group would be welcome.

Gender

The issues of gender differences in terms of obesity and response to anti-obesity treatment is an area that may require further study. More men than women are overweight (46% versus 32% in England in 1998) but a slightly higher proportion of women than men are obese (19% versus 17% from the same survey).[4] Gender differences also occur in terms of fat distribution. Men tend to have more frequent central (abdominal) obesity, whilst thighs and buttocks are the commonest body areas for fat deposition in women. Of these two types of fat distribution, central obesity is more likely to be associated with hyperlipidaemia, CHD, hypertension and impaired glycaemic control.[71] With the exception of two trials involving females only,[39,43] all included trials recruited participants of both sexes and, in general, there were larger proportions of female participants. None of the trials incorporated stratification of results according to gender. Future trials could usefully stratify results in this way to determine whether the treatment effects of anti-obesity drugs are different between men and women.

Other demographic variables

It is possible that factors such as ethnicity and social class may also influence patients' response to treatment for obesity. Asian people are considered to be particularly at risk of developing obesity[7] and, in general, the prevalence of obesity is inversely related to social class or household income, although this trend is more distinct in women.[4] Some of the trials included in this review reported the baseline distribution of different ethnic groups;[41,44,47,48] however, none presented results according to ethnic group, and none reported baseline distribution of social class or household income. It would be useful if future research could investigate the impact of treatment on different ethnic or social groups in order to help determine the best patients to target for anti-obesity pharmacotherapy.

Trials versus clinical practice

This review has identified some issues relating to the compatibility between trials and clinical practice in terms of patient characteristics and patient management.

Patient characteristics

In terms of patient characteristics, there are issues relating to the methods for recruitment in clinical trials and to the relationship between selection criteria used in trials as opposed to those used to select patients for treatment in clinical practice.

In many of the included trials, the methods used for recruiting patients were not described. Recruitment methods involving advertising may attract participants who wish to lose weight for cosmetic reasons. Such trials may not reflect the use of anti-obesity drugs in patients with identified risk factors such as hypertension, impaired glycaemic control and hyperlipidaemia, and may not be informative about the effectiveness of drugs in improving risk-factor profiles. Other recruitment strategies involve enlisting patients attending specialist obesity clinics. These patients may represent the most refractory cases, and may also underestimate the treatment effects that may be found in a more general population. It would be useful if future trials could incorporate selection criteria that reflect characteristics of people likely to be selected for treatment in clinical practice.

Prescribing guidelines recommend that sibutramine should be used in the management of patients with a BMI of 30 kg/m^2 or more, or in those with a BMI of 27 kg/m^2 or more in the presence of other risk factors (i.e. hypertension, diabetes and hyperlipidaemia).[33]

Of the 16 trials of sibutramine included in this review, ten incorporated participant selection criteria that reflected the above

recommendations,[41–43,46–49,51–53] four employed selection criteria that allowed inclusion of patients who did not meet the recommended criteria,[39,44,45,50] and in two it was not possible to judge because selection criteria relating to BMI were not given.[38,40]

For sibutramine trials that coincided with the recommendations, most reported statistically significant results in favour of the active drug relative to placebo in terms of weight loss or reduction in BMI for both diabetic[47,52,53] and non-diabetic participants.[41,42,48,49] Sibutramine also produced significantly more favourable results in terms of weight maintenance compared with placebo.[46,51] However, results for other outcomes such as those relating to glycaemic control and modification of lipid levels were less consistent.

It would be useful if future trials used participant inclusion criteria that were matched with recommended indications for drug use. Alternatively, baseline data and results could be stratified according to whether recruited patients met the recommended criteria or not.

Patient management

It is likely that the management of patients recruited for trials does not closely correspond to the management of patients in usual clinical practice. For example, trial participants receiving placebo probably experience more intensive management than would normally occur in clinical practice. Patients recruited to trials attend clinic more often and receive closer dietary supervision. Placebo-controlled RCTs in which all participants receive identical treatment, with the exception of the study medication, should give an indication of the effects of the active drug over and above the rest of the treatment package and the placebo effect. However, it may be useful if future trials could try to replicate the management of patients in everyday clinical practice, and attempt to assess the effectiveness of anti-obesity drugs combined with usual clinical management over and above usual clinical management without drugs.

For most obese people, obesity is a chronic condition with a tendency towards patterns of weight loss and weight regain over time. In light of this, longer-term data on the effectiveness and safety of sibutramine would be helpful. The longest study endpoint for published data included in this review was in a trial evaluating an 18-month weight maintenance programme.[51] The longest study endpoint for published trials of weight loss with sibutramine was 6 months.[41,42,47,48]

Sponsorship of trials

It should be noted that most of the trials included in this review were described as being sponsored by the manufacturer. In one case, the sponsorship was unclear, but it was apparent that the company assisted the research by supplying the study medication.[46]

Comparison with other systematic reviews

No other systematic reviews of sibutramine were identified.

Conclusions

Implications for clinical practice

Many of the trials included in this review demonstrated statistically significant differences between groups in terms of absolute weight loss, proportions of patients achieving at least 5% or 10% loss of initial body weight and weight maintenance in favour of sibutramine when compared with placebo. Sometimes the mean difference between treatment groups was small, and healthcare professionals involved in the care of obese patients will need to decide whether these differences are clinically significant. In addition, the possible adverse effects associated with the use of sibutramine should be taken into account. For sibutramine, weight loss appears to be dose-related; most of the regimens promoting statistically significant weight loss relative to placebo involved daily doses of 10–20 mg. Between-group differences in other outcomes (changes in lipid levels, indicators of glycaemic control and BP) were less consistent across trials in terms of statistical significance. In studies where the between-group difference for these outcomes was statistically significant, clinicians should judge whether the differences observed were of clinical importance.

The cost per QALY for sibutramine was estimated as £10,500.[54]

Recommendations for future research

In general, the methodological quality of included trials was moderate or good. However, some trials were under-powered. It would be useful if future studies had sufficient statistical power to detect between-group differences for both change in body weight and also changes in other cardiovascular risk indicators. It is recommended that ITT analysis is incorporated

into future trials; the optimum methods for achieving this are under debate.

Further research is required in both younger and older patients to assess the effectiveness and safety of sibutramine in these age groups. In addition, results could usefully be stratified by variables such as gender, ethnicity and social class in order to assist clinicians in identifying the types of patients most likely to benefit from treatment. In order to assist with generalisability of results, patient selection and management in trials should aim to match the criteria used in clinical practice.

Acknowledgements

This report was commissioned by the NHS R&D HTA Programme, project number 00/05/02.

The review team wish to thank the expert advisory panel for their useful and constructive comments on the review protocol and draft report (appendix 7). We are also most grateful to Julie Glanville, Information Manager at the NHS Centre for Reviews and Dissemination, for assistance with contacting authors of conference abstracts, to Caroline Horwood and Vanda Castle for secretarial support, and to Zoe Philips, Research Fellow at the Centre for Health Economics, University of York, for assistance with assessing the economic evaluation following finalisation of the price of sibutramine.

The views expressed are those of the authors, who are also responsible for any errors.

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Appendix 1

Search strategy

The search strategy below was used for the joint review of orlistat and sibutramine.

#1 explode "Obesity"/all subheadings
#2 "Body-Weight"/all subheadings
#3 "Hyperphagia"/all subheadings
#4 "Adipose-Tissue"/all subheadings
#5 weight or overweight or obese or obesity or antiobesity
#6 food or appetite or satiety
#7 adiposity or overeating
#8 hyperphagia or fat
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 orlistat
#11 xenical
#12 tetrahydrolipstatin
#13 sibutramine
#14 meridia in ti,ab
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

This strategy was used for the MEDLINE database and was adapted, as appropriate, for the other databases searched.

Appendix 2

Prescreen form

1. Paper (author and year)
2. Study design (eligible for inclusion: RCT)
3. Participants (eligible for inclusion: overweight/obese or maintaining weight loss)
4. Interventions (eligible for inclusion: sibutramine)
5. Outcomes (eligible for inclusion: body weight, fat content or fat distribution assessed at both baseline and post-intervention)
6. Language (eligible for inclusion: English, French, German, Dutch)
7. Decision:

Appendix 3

Data extraction table

(A) For published RCTs

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hansen *et al.*, 1999[38] ***Countries*** Denmark/UK ***Aim*** To evaluate the effect of sibutramine on weight loss and EE in obese patients ***Method of randomisation*** Not stated ***Outcomes*** Change in body weight; change in body composition (assessed by dual-energy X-ray absorptiometry scan); BP; HR; sensations of satiety, hunger, fullness and anticipated food consumption (assessed with VAS); EE (measured by indirect calorimetry during a 32-hour stay in a respiration chamber prior to and after 8 weeks of treatment); AEs ***Setting and length of treatment*** Setting not stated; EE assessments carried out under laboratory conditions; 8-week study	***Population*** Not stated ***Inclusion criteria*** Obese, otherwise healthy patients; stable weight (± 3 kg) for at least 3 months prior to the study ***Exclusion criteria*** Not stated	***Standard care for all patients*** No dietary restrictions were required of the patients and they were instructed not to change their food intake or physical activity C: placebo once daily for 8 weeks (n = 18) I: sibutramine 15 mg once daily for 8 weeks (n = 14)	**Data for completers** C: 18; I: 14 ***Gender*** (male/female) C: 4/14 I: 3/11 ***Age*** (mean ± SEM in years) C: 40.4 ± 2.1 I: 36.9 ± 2.6 ***Weight*** (mean ± SEM in kg) C: 98.0 ± 2.7 I: 103.4 ± 2.9 ***BMI*** (mean ± SEM in kg/m^2) C: 33.6 ± 0.7 I: 34.3 ± 0.7 ***Fat mass*** (mean ± SEM in kg) C: 37.4 ± 2.2 I: 41.0 ± 2.0 ***Fat-free mass*** (mean ± SEM in kg) C: 59.8 ± 2.2 I: 61.9 ± 2.3	***Statistical techniques*** Group means compared by Student's unpaired t test. Changes in EE tested by 2-way ANOVA of repeated measurement with treatment and time as factors. Predictors of changes in EE determined by forward stepwise regression **Results at 8 weeks:** ***Weight change*** (mean ± SEM in kg) C: +0.4 ± 0.4; I: –2.6 ± 0.5 $p < 0.001$ ***Change in fat mass*** (mean ± SEM in kg) C: –0.2 ± 0.3; I: –2.2 ± 0.4 $p < 0.001$ ***Change in fat-free mass*** (mean ± SEM in kg) C: +0.2 ± 0.2; I: –1.5 ± 0.4 $p < 0.001$ ***Change in 24-hour EE*** C: –2.5%; I: –2.6% ns When the changes in 24-hour EE were adjusted for changes in body weight, 24-hour EE decreased less in I (0.8%) than C (3.8%) ($p < 0.02$) Sibutramine significantly decreased both hunger and anticipated food consumption, and increased satiety scores ***Increase in DBP*** (mean ± SEM in mmHg) (baseline/endpoint) C: 72.2 ± 2.7/73.0 ± 2.2 I: 74.3 ± 3.1/81.4 ± 2.5 $p < 0.05$ No significant changes were observed in SBP in either group ***Change in HR*** (mean ± SEM in bpm) C: –1.7 ± 1.2; I: +7.1 ± 2.1 $p < 0.001$ Changes in HR were correlated with the changes in 24-hour EE (r = 0.41, $p < 0.05$)	In all, 6 patients did not complete the study: 2 due to AEs (migraine and cold); 2 did not attend the second chamber stay because of personal reasons; 1 left the study prematurely for occupational reasons; and 1 did not complete the second 24-hour measure of EE due to technical problems	***Study limitations, as noted by the study authors*** None stated ***Reviewer's comments*** One of the authors' conclusions, that sibutramine can cause weight loss without the need to restrict energy intake, may not fit with the obesity-management rationale of most clinicians (i.e. patients should be encouraged to modify their lifestyle as a concomitant measure to drug use) Number of patients randomised not stated. All reported data relates to completers ***Sponsorship*** Knoll Pharmaceuticals, Nottingham, UK

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Seagle *et al.*, 1998[39] ***Country*** USA ***Aim*** To determine the effect of sibutramine on metabolic rate and weight loss in moderately obese women ***Method of randomisation*** Not stated ***Outcomes*** Body weight; BMI; fat mass; fat-free mass; waist circumference; hip circumference; waist–hip ratio; BP; PR; RMR; adherence with dietary regimen; adherence with medication regimen; subjective food consumption ratings (assessed by VAS); AEs ***Setting and length of treatment*** Setting not stated; 8-week weight loss phase followed by 4-week maintenance phase	***Population*** Obese women recruited from the Denver metropolitan area by newspaper advertisements and flyers ***Inclusion criteria*** Age 18–45 years; BMI 28–40 kg/m^2; stable at current weight (± 2.3 kg) for at least 6 months ***Exclusion criteria*** Smoking; cardiovascular disorders; high BP; diabetes; thyroid dysfunction; any other disorder known to interfere with intermediary metabolism	***Standard care for all patients during weight loss phase*** Patients received individual instruction on following a 1200 kcal/day diet containing 50% of calories from carbohydrates, 30% from fat and 20% from protein. Patients were encouraged to become more physically active but were not given any specific activity goals C: placebo to be taken with 4 ounces of water at the same time each morning for 8 weeks (n = 16) I1: sibutramine 10 mg/day to be taken with 4 ounces of water at the same time each morning for 8 weeks (n = 17) I2: sibutramine 30 mg/day to be taken with 4 ounces of water at the same time each morning for 8 weeks (n = 16)	**Data for completers:** ***Gender*** All participants were female ***Age*** (mean ± SEM in years) C: 34.5 ± 1.7; I1: 34.2 ± 1.7; I2: 34.6 ± 1.7 ***Weight*** (mean ± SEM in kg) C: 86.7 ± 3.5; I1: 88.3 ± 3.3; I2: 89.5 ± 2.6 ***BMI*** (mean ± SEM in kg/m^2) C: 33.1 ± 1.0; I1: 32.7 ± 0.9; I2: 33.1 ± 1.0 ***Body fat*** (mean ± SEM as %) C: 45.5 ± 1.2; I1: 42.1 ± 1.3; I2: 44.3 ± 1.5 ***Fat mass*** (mean ± SEM in kg) C: 39.6 ± 2.4; I1: 37.1 ± 2.3; I2: 39.7 ± 2.4 ***Fat-free mass*** (mean ± SEM in kg) C: 46.6 ± 1.3; I1: 50.1 ± 1.5; I2: 49.0 ± 1.0 ***Waist circumference*** (mean ± SEM in cm) C: 92.6 ± 2.5; I1: 93.0 ± 2.0; I2: 89.0 ± 2.1 ***Hip circumference*** (mean ± SEM in cm) C: 115.7 ± 2.3; I1: 115.0 ± 2.6; I2: 118.4 ± 2.7	***Statistical techniques*** Repeated measures ANOVA used to determine differences due to treatment group and time as well as any group by time interaction. For changes in RMR, fat-free mass and fat mass were included as covariates in the repeated measures analysis **Results at 8 weeks (weight loss phase):** ***Change in body weight*** (mean ± SEM in kg) C: –3.3 ± 0.4; I1: –7.1 ± 0.7; I2: –7.4 ± 0.6 $p < 0.001$ for C vs I1 and C vs I2 ***Change in BMI*** (mean ± SEM in kg/m^2) C: –1.2 ± 0.2; I1: –2.6 ± 0.3; I2: –2.7 ± 0.2 $p < 0.05$ for C vs I1 and C vs I2 ***Change in fat mass*** (mean ± SEM in kg) C: –3.0 ± 0.4; I1: –4.3 ± 0.6; I2: –5.2 ± 0.6 $p < 0.05$ for C vs I1 and C vs I2 ***Change in fat-free mass*** (mean ± SEM kg) C: –0.3 ± 0.3; I1: –2.3 ± 0.4; I2: –2.4 ± 0.5 $p < 0.05$ for C vs I1 and C vs I2 ***Change in waist circumference*** (mean ± SEM in cm) C: –2.4 ± 0.6; I1: –4.7 ± 1.0; I2: –4.2 ± 0.8 ns ***Change in hip circumference*** (mean ± SEM in cm) C: –2.0 ± 1.0; I1: –5.2 ± 0.9; I2: –5.2 ± 0.8 $p < 0.05$ for C vs I1 and C vs I2 ***Change in waist–hip ratio*** (mean ± SEM) C: –0.008 ± 0.008; I1: –0.006 ± 0.010; I2: –0.002 ± 0.006 ns ***RMR results*** No statistically significant between-group differences for RMR, with or without adjustment for fat mass and fat-free mass ***≥ 5% weight loss*** C: 27%; I1: 80%; I2: 93% Note: values read from a graph	A total of 5/49 (10%) patients withdrew Of the 5, 2 relocated to another city and 2 had conflicts with the study scheduling ***Numbers of patients completing both the DB and weight-stabilisation periods*** C: 15; I1: 15; I2: 14 ***AEs*** There were no withdrawals due to AEs; most were mild or moderate. The most frequent AEs associated with sibutramine use were anorexia, nausea, CNS stimulation, dizziness, dry mouth, insomnia and rhinitis. One serious event occurred in a patient receiving placebo who was treated for a possible peptic ulcer. No deaths occurred during the study. No unusual effects were noted for laboratory parameters, vital signs, or ECG readings. No significant differences were noted for prolactin levels	***Study limitations, as noted by the study authors*** Although all patients received the same dietary instruction, actual energy intake was not quantified. It is possible that the sibutramine-treated patients experienced a decrease in appetite that decreased their actual energy intake to below 1200 kcal/day. Additionally, the placebo group may have had difficulty adhering to the 1200 kcal/day diet, thus consuming more. Such a discrepancy in energy intake could explain some of the difference in weight loss between groups The food consumption ratings were administered while the patient fasted during an office visit, and therefore it is possible that the true changes in appetite that may have occurred during the course of a patient's typical day were not captured ***Sponsorship*** Knoll Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Seagle et *al*., 1998**[39]		***Weight maintenance phase*** After 8 weeks of treatment, drugs were discontinued. Diet alone was used to maintain patients at their week 8 body weights for an additional 4 weeks	***Waist–hip ratio*** (mean ± SEM) C: 0.800 ± 0.015 I1: 0.811 ± 0.013 I2: 0.753 ± 0.013	***≥ 10% weight loss*** C: 0%; I1: 33%; I2: 28% Note: values read from a graph ***Hunger/satiety at 8 weeks*** No significant treatment effects were noted for evening hunger, evening satiety, sweet food craving, savoury food craving, carbohydrate craving, or carbohydrate snacking. However, a significant decrease in overall appetite was seen in I2 versus the other 2 groups ($p = 0.009$) **Results at 12 weeks (weight maintenance phase) – note that changes reported are from baseline:** ***Change in body weight*** (mean ± SEM in kg) C: –3.3 ± 0.5; I1: –6.4 ± 1.0; I2: –6.4 ± 0.5 $p < 0.05$ for C vs I1 and C vs I2 ***Change in BMI*** (mean ± SEM in kg/m^2) C: –1.2 ± 0.2; I1: –2.4 ± 0.4; I2: –2.4 ± 0.2 $p < 0.05$ for C vs I1 and C vs I2 ***Change in fat mass*** (mean ± SEM in kg) C: –3.6 ± 0.5; I1: –4.7 ± 0.7; I2: –5.0 ± 0.5 ns ***Change in fat-free mass*** (mean ± SEM in kg) C: +0.1 ± 0.3; I1: –1.3 ± 0.5; I2: –1.1 ± 0.4 ns ***Change in waist circumference*** (mean ± SEM in cm) C: –0.9 ± 0.9; I1: –4.7 ± 1.1; I2: –3.2 ± 0.8 $p < 0.05$ for C vs I1 ***Change in hip circumference*** (mean ± SEM in cm) C: –2.4 ± 1.0; I1: –4.7 ± 0.9; I2: –6.2 ± 0.7 $p < 0.05$ for C vs I2 ***Change in waist–hip ratio*** (mean ± SEM) C: +0.010 ± 0.011; I1: –0.008 ± 0.010; I2: +0.014 ± 0.006 ns ***RMR results*** No statistically significant between-group differences for RMR, with or without adjustment for fat mass and fat-free mass	No clinically significant treatment effects were observed for either supine SBP or DBP. However, mean dose-related increases in PR were observed for sibutramine relative to placebo. However, using one-way ANOVA, the changes in PR were not statistically significant between treatment groups at any time point	

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Weintraub et *al.*, 1991[40] ***Country*** USA ***Aim*** To assess the effectiveness and safety of 2 doses of sibutramine in obesity ***Method of randomisation*** Allocation method not stated. Patients were stratified according to a score based on the following variables: gender, family income (≥ $30,000/year or < $30,000/year), night-time snacking (yes or no), onset of obesity (18 years or older, 12–17 years, 11 years and younger), physician rating of motivation (great, moderate, some, none), and weight loss during run-in ***Outcomes*** Weight loss; percentage change in body weight; ECG; laboratory tests; adverse effects; adherence with drug regimen (assessed by pill count) ***Setting and length of treatment*** Setting not stated. Run-in of 3 weeks followed by 8-week DB phase	***Population*** Not stated ***Inclusion criteria*** Age 18–65 years; 130–180% of ideal body weight; women were eligible only if postmenopausal or surgically sterilised; sitting BP less than 140/90 mmHg with a concomitant HR of less than 100 bpm ***Exclusion criteria*** Any significant medical illness; abnormalities detected on ECG or by laboratory tests; use of prescribed, over-the-counter or investigational medications; participation in formal weight loss programme in the 3-month period prior to study; history of decreased platelet count; danger or difficulty in sibutramine use due to work schedule	***3-week run-in period for all patients*** A dietician devised an individualised calorie restriction plan for each patient, based on the patient's preferences and dietary habits, limited to 22–25 kcal/kg ideal body weight/day. All patients were urged to eat breakfast. A behaviour modification programme was started and patients were instructed to increase physical activity levels ***Standard care for all patients during DB study*** As above C: placebo, once daily, after breakfast, for 8 weeks (n = 20) I1: sibutramine 5 mg, once daily, after breakfast, for 8 weeks (n = 19) I2: sibutramine 20 mg, once daily, after breakfast, for 8 weeks (n = 21)	***Gender*** (male/female) C: 6/14 I1: 5/14 I2: 7/14 ***Age*** (mean ± SD in years) C: 46.6 ± 8.7 I1: 47.6 ± 8.0 I2: 45.4 ± 7.6 ***% Ideal body weight*** (mean ± SD) C: 153 ± 10 I1: 154 ± 13 I2: 157 ± 12	***Statistical techniques*** Fisher protected least-squares difference method, ANOVA, and linear regression (treating the 3 doses as if they were equally spaced). Untransformed and square-root transformed dose values were examined in the regression analysis ***Weight change during run-in*** (mean ± SD in kg) C: –1.2 ± 1.5 I1: –1.6 ± 1.8 I2: –0.7 ± 1.1 ***Weight change from end of run-in to week 8*** (mean ± SD in kg) C: –1.4 ± 2.1 (–1.3% ± 2.2%) I1: –2.9 ± 2.3 (–3.0% ± 2.3%) I2: –5.0 ± 2.7 (–5.1% ± 2.8%) p < 0.05 for C vs I1, C vs I2, and I1 vs I2 Results of regression analysis indicated a significant relationship between weight loss and dose	***AEs*** – Neither BP nor PR changed dramatically during the course of the study. However, there was an increase in HR in all groups between either screening or baseline and week 8. 4 participants had an increase of either 10 bpm or to a resting HR more than 90 bpm on at least 1 occasion (2 in C, 1 in I1, and 1 in I2) – No clinically significant ECG abnormalities were noted in any group; 3 patients in I2 had increased numbers of premature contractions without any symptoms or cardiac signs – Patients in I2 had an increased frequency of headache – 1 patient in I1 and 7 in I2 made 27 reports of sleep difficulty (problems with falling asleep, staying asleep and short sleep duration). In most cases, patients were untroubled or welcomed the changes in their sleep pattern – 6 patients in I2 made 13 reports of irritability – 5 patients in C, 6 in I1 and 6 in I2 complained of a dry mouth – Skin reactions (rash or dryness) occurred equally across groups – Complaints of minor AEs were frequent and encompassed all patients ***Withdrawals*** In all, 5 patients withdrew due to AEs: C: 1 (skin rash and hives) I1: 1 (headache, dizziness, nausea, abdominal cramps and faintness) I2: 3 (1 depression, fatigue, headache and early morning wakening; 1 abdominal pain, heartburn, gas; 1 rash, panic attacks, numbness, tingling of hands and feet) ***Laboratory data*** No specific laboratory abnormalities related to liver, kidneys, or bone marrow were noted. However, some patients had minor abnormalities in their serum transaminase levels at screening and baseline No clear patterns occurred in the ratings of hunger, fullness, appetite and diet difficulty ***Adherence*** Of completers, 93% took 90% or more of the prescribed doses of medication. Weight loss in C and I1 decreased with decreasing adherence, but in I2 there was little difference in weight loss between those adhering 100% and those adhering less. At the same level of adherence, weight loss in C was less than I1, and that in I1 was less than I2. Adherence among withdrawals averaged 91.4%	***Study limitations, as noted by the study authors*** The optimum dose of sibutramine was not defined. Sibutramine should be studied further at other doses and with longer F/U ***Sponsorship*** Boots Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Finer *et al.*, 2000[44] ***Country*** UK ***Aim*** To investigate the efficacy and tolerability of sibutramine in reducing body weight and improving glycaemic control in obese patients with type-2 diabetes ***Method of randomisation*** Not stated ***Outcomes*** Body weight; BMI; body composition (assessed using dual-energy X-ray absorptiometry); waist–hip ratio; fasting blood glucose and insulin levels; test meal study for glucose and insulin levels; glycosolated haemoglobin; mean peak glucose concentrations; BP; PR; ECG; adherence with dietary advice (assessed using 5-point categorical scale); adverse effects ***Setting and length of treatment*** 2 hospital obesity/diabetic clinics in the UK. Run-in of 1 week followed by 12-week DB trial	***Population*** Patients attending diabetes outpatient clinics ***Inclusion criteria*** Age 30–65 years, BMI > 26 kg/m^2 and ≤ 35 kg/m^2; diagnosis of type-2 diabetes for at least 6 months; fasting blood glucose > 7.0 mmol/l and < 12.0 mmol/l on 3 occasions during the month prior to study entry; women of childbearing potential were eligible provided they were taking adequate contraceptive measures; patients receiving thyroxine or diabetes medication were eligible if the dosage had been stable for the previous 3 months ***Exclusion criteria*** Type-1 diabetes; obesity of endocrine origin other than that associated with type-2 diabetes; supine	***1-week run-in period for all patients*** Patients were interviewed by a dietician, given a set of healthy eating guidelines to follow throughout the study, and encouraged to follow dietary recommendations for diabetic persons. Each patient was advised to follow a customised, reduced-calorie diet, with an energy deficit of 500 kcal/day. Each patient completed a 3-day diet diary from which reported energy intake and proportions of protein, fat and carbohydrate were calculated ***Standard care for all patients during DB study*** Dietary regimen as above. Dietary advice was provided throughout the 12 weeks	***Gender*** (male/female) C: 20/24 I: 23/24 ***Age*** (mean ± SD (range) in years) C: 54.1 ± 7.5 (37–65) I: 53.7 ± 8.4 (34–65) ***Race*** (white/black) C: 33/11 I: 39/8 ***Mean weight*** ((range) in kg) C: 82.5 (63.3–114.8) I: 84.6 (63.7–117.1) ***BMI*** (mean ± SD (range) in kg/m^2) C: 31.0 ± 2.7 (26.1–35.1) I: 30.6 ± 2.7 (25.8–36.0) ***Glycosolated haemoglobin*** (mean ± SD) C: 9.4 ± 1.3% I: 9.5 ± 1.8% ***Treatment for diabetes*** Diet alone: C = 4; I = 9 Insulin: C = 12; I = 10 Metformin: C = 16; I = 13 Sulphonylureas: C = 24; I = 25	***Statistical techniques*** All tests were 2-tailed. Changes from baseline for efficacy and vital sign variables were analysed by ANOVA with factors for treatment group, centre and treatment group by centre interaction. Body weight measures were log transformed prior to analysis; glucose and insulin were rank transformed **Results at 12 weeks:** ***Dietary adherence scores*** Changed little in either group; did not differ between groups ***Dietary intake variables*** Groups did not differ for intake of calories, protein, fat and carbohydrate ***Patients with increase or decrease in dose of anti-diabetic therapy during the study*** C: 8/44 (18%); I: 5/47 (11%); ns ***Mean weight change*** (in kg by LOCF analysis) C: –0.1 (–0.7 to 0.4); I: –2.4 (–3.0 to –1.8) $p < 0.001$ ***Mean change in BMI*** (kg/m^2) C: –0.1; I: –0.9 $p < 0.001$ ***Patients losing > 5% of initial weight*** C: 0%; I: 19% $p < 0.001$; 95% CI, 9 to 30 ***Body composition based on data from 38 patients in C and 39 patients in I*** ***Change in fat mass*** (kg) C: –0.2; I: –1.8 $p < 0.001$ ***Change in fat-free mass*** (kg) C: –0.3; I: –0.8 ns	***Completers*** C: 40/44 (91%); I: 43/47 (91%) ***Withdrawals during DB phase*** AEs: C = 2; I = 3 Lost to F/U: C = 1; I = 0 Withdrew consent: C = 1; I = 1 Total: C = 4; I = 4 ***AEs reported by:*** C: 45/47 (96%) patients; I: 42/44 (95%) patients ***Most common AEs*** Headache: C = 19; I = 14 Constipation: C = 13; I = 13 Dry mouth: C = 5; I = 10 Infection: C = 1; I = 8 Pharyngitis: C = 4; I = 8 Dizziness: C = 6; I = 6 AEs were mild or moderate in severity for 97% of those reported in I and 99% of those reported in C 7% of AEs in I and 1% in C were reported as probably due to treatment ***Withdrawals due to AEs*** C: 2 (1 for giddiness and vomiting, 1 for headache) I: 3 (1 each for dizziness, insomnia and diarrhoea)	***Study limitations, as noted by the study authors*** Longer-term and larger studies are required to better elucidate the magnitude and durability of the benefits of weight reduction with sibutramine on glycaemic control in obese patients with type-2 diabetes ***Sponsorship*** Knoll Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Finer *et al.*, 2000**[44]	DBP > 100 mmHg; concomitant use of any drug that might affect appetite or body weight	C: placebo once daily for 12 weeks (n = 44) I: sibutramine 15 mg once daily for 12 weeks (n = 47)		***Waist–hip ratio*** Reductions were seen at 12 weeks in both groups, but there were no significant differences between groups ***Glycaemic control*** Fasting blood glucose levels decreased relative to baseline in I patients (0.3 mmol/l) and increased in C patients (1.4 mmol/l). Mean peak blood glucose level after the test meal decreased by 1.1 mmol/l from baseline to endpoint in I and increased by 0.5 mmol/l in C (p = 0.04, difference in means –1.6: 95% CI, –3.3 to –0.1). Fasting insulin levels in patients not receiving exogenous insulin showed a median decrease at endpoint of 1.9 mU/l in I and a rise of 0.5 mU/l in C. Mean glycosolated haemoglobin values decreased by 0.3% units in I but did not change in C. In all, 15/45 (33%) of I patients experienced a decrease in glycosolated haemoglobin levels of ≥ 1% at endpoint compared with 2/41 (5%) patients in C (p < 0.05) A greater decrease in glycosolated haemoglobin was associated with greater reduction in weight in I patients ***Vital signs*** No significant differences were found between groups for changes in BP. Radial PRs increased by 7.5 bpm in I patients and 0.2 bpm in C (p = 0.005). ECG HR changes were consistent with PR changes. No clinically significant conduction or rhythm abnormalities were observed on ECG		

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Hanotin et *al.*, 1998[45] ***Country*** France ***Aim*** To compare the efficacy and tolerability of sibutramine versus dexfenfluramine in promoting weight loss in patients with obesity ***Method of randomisation*** Not stated; randomised in blocks of 4 (2 sibutramine and 2 dexfenfluramine patients) ***Outcomes*** Change in body weight; percentage weight loss; changes in waist and hip circumferences; BP; HR; ECG; standard laboratory assessments; AEs; adherence with dietary regimen (assessed with VAS); adherence with drug regimen (assessed by counting returned capsules) For change in body weight, the predetermined range for equivalence between groups was –2 kg to +2 kg ***Setting and length of treatment*** 38 centres; 12-week trial	***Population*** Not stated ***Inclusion criteria*** Hospital outpatients or patients in private practice; age 18–65 years; BMI of at least 27 kg/m^2 ***Exclusion criteria*** Obesity of endocrine origin; type-1 or type-2 diabetes mellitus receiving insulin or oral hypoglycaemic agents; supine DBP > 100 mmHg; any significant illness; significant ECG or laboratory abnormality; more than borderline depression (assessed by the Clinical Global Impression scale); > 3 kg weight loss in previous 3 months; use of medication that could alter body weight or interfere with absorption, metabolism or excretion of the study medications	***1–2-week run-in period for all patients*** For screening only ***Standard care for all patients during DB study*** Adjunctive dietary therapy and behavioural modification advice given in accordance with the usual practice of the investigator I1: dexfenfluramine 15 mg twice daily for 12 weeks (n = 114) I2: sibutramine 10 mg once daily for 12 weeks (n = 112) For blinding purposes, each white dexfenfluramine capsule was enclosed in a brown capsule to match the sibutramine capsules. Matched brown placebo capsules were also provided to sibutramine-treated patients	***Gender*** (male/female) I1: 8/106 I2: 11/101 ***Age*** (mean ± SEM in years) I1: 38.8 ± 1.1 I2: 38.9 ± 1.1 ***Weight*** (median (range) in kg) I1: 86.0 (63–142.5) I2: 84.0 (66–167.5) ***BMI*** (mean ± SEM in kg/m^2) I1: 33.7 ± 0.5 I2: 33.3 ± 0.5	***Statistical techniques*** Weight loss at 3 months was analysed according to both ITT (LOCF) and completers' data. 2 one-sided, 2-sample t tests were used. 90% CIs were reported. For other measures of efficacy and safety, results were presented in terms of 95% CI for the difference between the 2 groups. However, withdrawal rates and safety variables of most interest were compared between groups using the 90% CI for the RR. No factor for centre was included in the analysis as the median number of patients recruited at each centre was < 8 patients **Results at 12 weeks:** ***Weight change*** (mean ± SEM in kg by ITT analysis) I1: –3.2 ± 0.3; I2: –4.5 ± 0.4 90% CI, –2.1 to –0.5 ***Weight change*** (mean ± SEM in kg for completers) I1: –3.6 ± 0.3; I2: –4.7 ± 0.4 90% CI, –1.9 to –0.3 ***Mean % weight change*** (by ITT analysis) I1: –3.7; I2: –5.2 90% CI, –2.4 to –0.6 ***Mean % weight change*** (for completers) I1: –4.2; I2: –5.4 90% CI, –2.2 to –0.3 ***> 5% loss of initial weight*** (by ITT analysis) I1: 34%; I2: 46% ***> 5% loss of initial weight*** (for completers) I1: 38%; I2: 48% As a secondary analysis, the 2 treatments were compared under the conventional null hypothesis of equality (as opposed to the equivalence range predetermined for this study of –2 kg to +2 kg). Weight loss (ITT) in I2 patients was significantly	***Overall withdrawals*** 29/226 (13%) patients ***Reasons for withdrawal per group (I1/I2)*** AEs: 1/6 Lack of efficacy: 3/2 Other reasons: 5/2 The overall risk of withdrawal was significantly higher in the dexfenfluramine group than in the sibutramine group (90% CI, 0.28 to 0.95) ***ITT analysis*** (based on 224/226 (99%) patients) I1: 112; I2: 112 ***Completers' analysis*** (based on 195/226 (86%) patients) I1: 94; I2: 101 ***Total number of AEs reported*** I1: 250; I2: 233 ***Total number of patients reporting AEs*** I1: 90; I2: 84 ***Reasons for withdrawal in I1*** 1 withdrawal each for: articular pain; asthenia; dizziness; epigastralgia; facial erythema/conjunctivitis; headache; hypotension/ nervousness; sciatica; traumatic vertebral fracture (n = 2 for nausea/vomiting/vertigo)	***Study limitations, as noted by the study authors*** None stated ***Sponsorship*** Knoll Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Hanotin *et al.*, 1998**[45]				greater than I1 ($p < 0.05$). Patients in I2 also had a statistically significant greater mean reduction in BMI, and a significantly greater proportion of them lost at least 5% of baseline body weight, or lost at least 0.45 kg/week, relative to I1 ***Mean decrease in waist/hip circumference*** (cm) I1: 4.0/2.7; I2: 4.5/3.7 Changes in waist–hip ratio were not statistically significant No significant differences were found at endpoint between groups with regard to ability to follow the diet ***Reductions in triglycerides*** I1: –0.12 mmol/l (8%) I2: –0.2 mmol/l (14%) 95% CI, –0.25 to 0.08 ***Reductions in total cholesterol*** I1: –6.3%; I2: –4.4% ***Mean change in SBP*** (mmHg) I1: +0.6; I2: +0.9 95% CI, –2.7 to 3.3 ***Mean change in DBP*** (mmHg) I1: –1.1; I2: +0.4 95% CI, –1.0 to 4.0 ***Mean change in PR*** (bpm) I1: –0.9; I2: +3.6 95% CI, 2.3 to 6.6 Mean HR, measured at week 12 from the ECG, was comparable with mean PR. No other clinically significant ECG changes were noted Median adherence with drug regimen was > 95% in both groups ***Weight regain 4 weeks after stopping treatment*** (mean ± SD) I1: 0.8 ± 1.6 kg (n = 92); I2: 0.5 ± 1.6 kg (n = 96) 95% CI, –0.7 to 0.2	***Reasons for withdrawal in I2*** 1 withdrawal each for: abdominal pain; allergic urticaria; depression; headache/thoracic pain; migraine; nausea/ dizziness Articular pain, sciatica, traumatic vertebral fracture and depression were defined as "serious adverse effects not considered to be related to study therapy" ***Most commonly reported AEs*** (no. of patients reporting: I1/I2) Constipation: 4/18 Flu syndrome: 11/18 Dry mouth: 11/15 Headache: 13/15 Asthenia: 16/7 Abdominal pain: 8/6 Insomnia: 9/6 Nausea: 7/6 Pharyngitis: 6/6 Infection: 10/3 Diarrhoea: 12/1 No clinically significant deleterious changes in laboratory assessments were noted for either group	

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Walsh *et al.*, 1999[43] ***Country*** UK ***Aim*** To assess the effect of sibutramine on weight loss, resting EE and adrenaline-induced thermogenesis in obese female patients ***Method of randomisation*** Not stated ***Outcomes*** Change in body weight; waist and hip circumference; body fat mass; percentage body fat (calculated as (0.439 × waist) + (0.221 × age) –9.4); FPG and insulin; cardiac output measurement (assessed by ultra-sound); REE; AEE (assessed during 30 minutes infusion of adrenaline, 25 ng/minute per kg ideal body weight); adherence with drug regimen (assessed by patient self-report and counting returned capsules); AEs	***Population*** Female patients recruited by local advertisement ***Inclusion criteria*** Age 18–65 years; BMI 30–44 kg/m^2; patients taking diuretic and thyroid preparations were eligible if stabilised for 3 and 6 months respectively prior to study ***Exclusion criteria*** DBP > 95 mmHg; resting HR greater than 100 bpm; unstabilised (< 3 months) antihypertensive therapy; obesity of endocrine origin; presence of any other significant medical illness; use of anorectic agents, laxatives or other medications which might alter body weight; diabetes; > 3 kg weight loss in the previous 3 months; pregnancy or risk of pregnancy	***Standard care for all patients*** Dietary counselling for a diet of 30% fat and energy content, set at 600 kcal/day energy deficit. Patients were provided with personalised diet sheets and advised how to use them C: placebo, once daily, prior to breakfast, for 12 weeks (n = 9) I: sibutramine 15 mg, once daily, prior to breakfast, for 12 weeks (n = 10)	***Gender*** All patients were female ***Age*** (mean ± SD in years) C: 44.1 ± 7.2; I: 48.3 ± 8.0 ***Weight*** (mean ± SD in kg) C: 85.2 ± 10.9; I: 93.9 ± 13.5 ***BMI*** (mean ± SD in kg/m^2) C: 34.5 ± 3.5; I: 34.4 ± 3.9 ***Waist circumference*** (mean ± SD in cm) C: 102.1 ± 9.9; I: 105.2 ± 8.0 ***Hip circumference*** (mean ± SD in cm) C: 116.4 ± 10.5; I: 119.9 ± 10.0 ***Waist–hip ratio*** (mean ± SD) C: 0.88 ± 0.08; I: 0.88 ± 0.06 ***Body fat*** (% body weight; mean ± SD) C: 45.2 ± 4.5; I: 47.5 ± 3.5 ***Body fat*** (mean ± SD in kg) C: 38.85 ± 8.6; I: 44.7 ± 8.5 ***Fat-free mass*** (mean ± SD in kg) C: 46.4 ± 3.5; I: 49.1 ± 6.1 ***Fasting insulin*** (mean ± SD in mU/l) C: 11.0 ± 3.8; I: 11.5 ± 5.1 ***Insulin/glucose ratio*** (mean ± SD) C: 2.1 ± 0.7; I: 2.1 ± 0.9 There were no statistically significant differences between groups for any of the above variables, nor for REE and adrenaline-stimulated EE and haemodynamics	***Statistical techniques*** Comparability of 2 groups assessed by 2-sample t test. Data that were not normally distributed were assessed by parametric tests if appropriate transformation was possible, but if not the data were assessed by the Mann–Whitney U test. The relationship between change in EE and change in fat-free mass and body weight were analysed by the Spearman rank correlation test for non-parametric data and by the Pearson method for parametric data. The difference between regression slopes for changes in REE and changes in fat-free mass were calculated according to Armitage and Berry tests **Results at 12 weeks:** ***Adherence with drug regimen*** Assessed as 100% % ***Weight change*** (mean ± SD) C: –5.1 ± 4.4; I: –8.1 ± 3.8 ns % ***Change in waist circumference*** (mean ± SD) C: –1.4 ± 5.7; I: –7.0 ± 6.6 ns % ***Change in hip circumference*** (mean ± SD) C: –2.7 ± 3.4; I: –2.6 ± 3.7 ns % ***Change in waist–hip ratio*** (mean ± SD) C: +1.4 ± 6.1; I: –4.3 ± 7.8 ns % ***Change in % body fat*** (mean ± SD) C: –1.3 ± 5.7; I: –6.7 ± 6.5 ns	All 19 patients completed the study No significant AEs were reported in either group	***Study limitations, as noted by the study authors*** Numbers too small to achieve statistically significant difference between groups for analyses of body morphological parameters ***Sponsorship*** Knoll Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Walsh *et al.*, 1999**[43] ***Setting and length of treatment*** Thermogenic challenge carried out under laboratory conditions, other details of setting not stated; 12-week trial			All patients had elevated total cholesterol (5.2–7.8 mmol/l) or total triglycerides (2.3–5.6 mmol/l) 1 patient took bendrofluazide during the study (dose unchanged)	% ***Change in body fat mass*** (mean ± SD) C: –6.3 ± 7.8; I: –14.2 ± 7.8 p = 0.04 % ***Change in fat-free mass*** (mean ± SD) C: –3.8 ± 5.1; I: –2.6 ± 5.8 ns % ***Change in fasting insulin*** (mean ± SD) C: –8.3 ± 46.2; I: –27.8 ± 24.2 ns % ***Change in insulin:glucose ratio*** (mean ± SD) C: –5.9 ± 52.0; I: –26.3 ± 25.2 ns There were no statistically significant differences between groups at 12 weeks for the following: % change in REE, % change in REE/kg body weight, % change in REE/kg fat-free mass, AEE (kcal/24 hour), AEE/kg body weight In absolute terms, there was a non-significant between-group difference in decrease in REE. The increased weight loss in I was associated with an increase in the fat-free mass-adjusted REE (2.2 ± 16.1%) unlike the expected decrease in C (5.8 ± 9.5%) (p = 0.11). There was some suggestion (p = 0.09) that the usual positive correlation between weight loss and decline in REE was lost in I (r = –0.30) compared with C (r = 0.35). There was a negative correlation between loss of fat-free mass and decline in REE/kg fat-free mass (p = 0.029) which was not evident in C. Adrenaline-induced EE was similar in the 2 groups at 12 weeks and there were no significant cardiovascular changes between the 2 groups		

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Fanghanel *et al.*, 2000[42] ***Country*** Mexico ***Aim*** To evaluate the safety and efficacy of sibutramine in obese patients over a period of 6 months ***Method of randomisation*** Computer-generated list prepared in 12 different blocks of 10 ***Outcomes*** Body weight; BMI; waist circumference; waist–hip ratio; appetite; satiety; diet adherence (last 3 assessed with VAS); medication adherence (assessed by counting returned capsules); AEs; blood cytology; blood chemistry; urinalysis; ECG ***Setting and length of treatment*** Mexico, outpatients; 6-month trial	***Population*** Mexican patients attending an endocrinology clinic at a general hospital ***Inclusion criteria*** Age 16–65 years; BMI > 30 kg/m^2 ***Exclusion criteria*** Endocrine diseases other than type-2 diabetes mellitus; uncontrolled hypertension; autoimmune diseases; ischaemic heart disease; arrhythmia; pregnancy; lactation; psychosis; use of drugs acting on the central nervous system, cathartics, thyroid replacement or diuretics	***Standard care for all patients*** Patients were recommended to consume a diet of 30 kcal/kg a day of ideal body weight, containing 50% of calories from carbohydrates, 30% from fats and 20% from proteins. Patients received a list of recommended food portions and the possible combinations. Patients received the dietetic advice 15 days before starting medication C: placebo daily for 6 months (n = 54) I: sibutramine 10 mg daily for 6 months (n = 55)	***Gender*** (male/female) C: 5/49 I: 4/51 ***Age*** (mean ± SD in years) C: 39.48 ± 10.26 I: 38.09 ± 10.11 ***Weight*** (mean ± SD in kg) C: 86.41 ± 12.92 I: 87.53 ± 16.0 ***BMI*** (mean ± SD in kg/m^2) C: 35.51 ± 4.99 I: 36.14 ± 5.07	***Statistical techniques*** ITT ANOVA for repeated measures looking for the effect of repetition and for the interaction between repetition and medication, and the intragroup comparison of baseline values with those at endpoint by paired Student's t test. The same analysis was performed for LOCF of the endpoints where the last observation replaced the missing values (included patients who completed at least 1 month of treatment with the corresponding endpoint evaluation). A further analysis was done assuming that patient withdrawals were non-responders (losing < 5% of initial weight). The missing data were calculated using regression curve estimation obtained from the non-responders data. Rate of patients with 5% and 10% loss from baseline per group was compared using Kaplan–Meier statistics, including the inverse of the survival curve. ORs for 5% and 10% responders were calculated. For other interval measurements, intragroup comparisons were analysed with the paired Student's t test, while the intergroup comparisons were performed using the unpaired Student's t test. For intergroup nominal data, the chi-squared test was used with continuity correction in the 2 × 2 tables **Results at 6 months:** ***Patient adherence with medication*** Estimated to be at least 90% The ITT ANOVA for multiple measures of body weight, BMI and waist circumference showed the effect of time (months) and interaction of the effect of time with type of medication (p < 0.001). For the waist–hip ratio, the analysis showed the effect of time (p < 0.001) but not of medication (p > 0.05). The ANOVA for repeated measures using LOCF produced similar results to the ITT analysis ***Patients losing 5% of initial body weight*** (by ITT analysis) C: 21/44 (47.7%); I: 34/40 (85%) ***Patients losing 5% of initial body weight*** (by LOCF analysis) C: 21/52 (40.4%); I: 37/51 (72.55%) The OR for I to achieve the 5% goal was 1.8 (95% CI, 1.24 to 12.6) ***Mean weight change*** (in kg by ITT analysis) (95% CI) C: –4.03 (2.74 to 5.32); I: –8.61 (7.06 to 10.17) ***Mean weight change*** (in kg by LOCF analysis) (95% CI) C: –3.56 (2.41 to 4.7); I: –7.52 (6.15 to 8.9)	Patients were withdrawn by investigators if they became pregnant, presented with a concomitant severe disease, suffered severe AEs, withdrew their informed consent or failed to attend clinic appointments ***Completers*** C: 44/54 (81%) I: 40/55 (73%) ***Lost to F/U*** C: 9/54 (17%) I: 11/55 (20%) ***Left trial due to AEs*** C: 1/54 (2%) I: 2/55 (4%) ***Number of AEs*** Dry mouth: C = 10, I = 14 Significant increase in BP: C = 11, I = 5 Significant increase in HR: C = 1, I = 5 Constipation: C = 0, I = 5 Insomnia: C = 0, I = 2 Urinary tract infection: C = 2, I = 1 Headache: C = 1, I = 1 Hypersomnia: C = 1, I = 1	***Study limitations, as noted by the study authors*** The experience of adverse effects in the sibutramine group could lead to the suspicion that these patients were taking the active drug rather than placebo ***Reviewer's comments*** Unclear how the ITT analysis differs from LOCF analysis ***Sponsorship*** Knoll Pharmaceuticals

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Fanghanel *et al.*, 2000**[42]				**% *Baseline weight remaining*** (mean ± SD by ITT analysis) (95% CI) C: 95.23 ± 5.01 (93.83 to 96.64) I: 90.11 ± 4.94 (88.66 to 91.56) **% *Baseline weight remaining*** (mean ± SD by LOCF analysis) (95% CI) C: 95.81 ± 4.85 (94.56 to 97.06) I: 91.33 ± 5.11 (90.0 to 92.67) ***Mean change in BMI*** (in kg/m^2 by ITT analysis) (95% CI) C: –1.66 (1.12 to 2.19); I: –3.59 (2.97 to 4.22) ***Mean change in BMI*** (in kg/m^2 by LOCF analysis) (95% CI) C: –1.46 (0.99 to 1.93); I: –3.14 (2.58 to 3.69) ***Mean change in waist circumference*** (in cm by ITT analysis) (95% CI) C: –4.69 (3.11 to 6.27); I: –8.09 (5.88 to 10.29) ***Mean change in waist circumference*** (in cm by LOCF analysis) (95% CI) C: –4.35 (2.93 to 5.78); I: –6.81 (4.78 to 8.83) ***Mean change in waist–hip ratio*** (by ITT analysis) (95% CI) C: –0.028 (0.014 to 0.043); I: –0.021 (0.005 to 0.038) ***Mean change in waist–hip ratio*** (by LOCF analysis) C: –0.025 (0.012 to 0.038); I: –0.017 (0.003 to 0.031) ***Rate of patients losing 10% of initial weight*** (by ITT analysis) C: 4/44 (9.1%); I: 18/40 (45%) ***Rate of patients losing 10% of initial weight*** (by LOCF analysis) C: 4/52 (7.7%); I: 19/51 (37.3%) OR for I to achieve 10% goal was 4.84 (95% CI, 1.77 to 13.25) Survival analysis of responders showed that the difference in the cumulative incidence of the event (5% loss of initial weight) was significant ($p < 0.01$). Similar results were obtained for 10% responders Endpoint body weight correlated well with baseline value in the non-responders when considering I and C together ($r > 0.95$) In I patients, appetite reduced significantly from the first month through to the end of the trial. I patients also had increased satiety in the first 3 months and a better adherence with the diet during the first month. C patients had significantly less appetite during the first and fifth months of treatment and did not have any significant changes in satiety or diet adherence	Most of the adverse effects in I patients occurred during the first 2 months of treatment ANOVA for repeated measures of SBP and DBP did not show any effect of treatment, time or interaction of treatment with time For HR, ANOVA for repeated measures showed an effect of time ($p < 0.05$) but not of treatment or interaction of treatment with time Paired ECGs did not show significant variations in I. C patients had small but statistically significant changes in HR and ST segment ($p < 0.05$) ***Clinical laboratory tests*** The intragroup analysis (before vs after) showed significant differences in monocytes, uric acid, creatinine, calcium, cholesterol, triglycerides, HDL and LDL for I. C presented significant changes in uric acid, creatinine, calcium and alkaline phosphatase	

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Cuellar *et al.*, 2000[48] ***Country*** Mexico ***Aim*** To evaluate the safety and efficacy of sibutramine in obese patients over a period of 6 months ***Method of randomisation*** Computerised list of random numbers; opaque sealed envelope containing drug code ***Outcomes*** Change in body weight; proportions of patients with 5% and 10% loss of initial weight from baseline; change in BMI; waist circumference; waist–hip ratio; ECG; HR; BP; appetite, satiety, adherence with diet (last 3 assessed with VAS); adherence with drug regimen (assessed by counting returned capsules); blood cytology; blood chemistry; urinalysis; AEs A loss of 5% of initial body weight was considered clinically significant ***Setting and length of treatment*** Mexico; 6 months	***Population*** Outpatients attending Mexican social security centre ***Inclusion criteria*** Age 16–65 years; BMI > 30 kg/m^2 ***Exclusion criteria*** Endocrine disease other than type-2 diabetes; uncontrolled hypertension; secondary hypertension; autoimmune disease; ischaemic heart disease; arrhythmia; pregnancy; lactation; psychosis; use of drugs acting on the central nervous system, cathartics, thyroid supplements or diuretics	***Standard care for all patients*** Patients were advised to follow a diet of 30 kcal/kg ideal body weight/day. The diet contained 50% of calories from carbohydrates, 30% from fats and 20% from proteins. Patients received a list of allowed and not-allowed foods with the recommended portions and possible combinations. All patients received printed material and brief dietary counselling C: placebo (matched in appearance to the active drug) once daily for 6 months (n = 34) I: sibutramine 15 mg daily for 6 months (n = 35)	***Gender*** (male/female) C: 7/27; I: 2/33 ***Age*** (mean ± SD in years) C: 38.62 ± 9.12 I: 38.44 ± 10.09 ***Weight*** (mean ± SD in kg) C: 90.07 ± 18.66 I: 85.96 ± 11.78 ***BMI*** (mean ± SD in kg/m^2) C: 35.97 ± 6.96 I: 35.54 ± 4.21 ***Race*** (caucasian/Mestizo/Indian) C: 0/33/1; I: 7/27/1 ***Physical activity*** (light/moderate/severe) C: 24/9/1; I: 32/2/1 ***Current tobacco use*** C: 16; I: 15 ***Concomitant chronic diseases reported by the patients at the beginning of the trial*** (hypertension/type-2 diabetes/dyslipidaemia) C: 4/4/2; I: 4/2/2 ***Concomitant chronic diseases found in physical examination and laboratory tests*** (hypertension/type-2 diabetes/hypercholesterolaemia/hypertriglyceridaemia) C: 4/6/4/13; I: 4/8/2/12	***Statistical techniques*** ITT (defined as 6-month completers) ANOVA for repeated measures looking for the effect of repetition and for the interaction between repetition and study medication, and the intragroup comparison of the values at baseline with those at 6 months analysed by paired Student's t test. Similar analysis performed with LOCF (included patients who completed at least 1 month of treatment with the corresponding endpoint evaluation). Rate of patients achieving 5% and 10% loss from baseline weight per group was compared using the Kaplan–Meier statistics, including the inverse of the survival curve. OR was calculated for sibutramine-treated patients with a loss of 5% and 10% of initial weight with respect to patients given placebo. For other interval measurements, the intragroup comparisons were tested with paired Student's t test, and intergroup comparisons were performed using the unpaired Student's t test, and, in the case of nominal scales in the intergroup comparisons, the chi-squared test, with continuity correction in the 2 × 2 tables, was used The overall adherence with the drug regimen was estimated as at least 90% ITT ANOVA for multiple measures of body weight, BMI, waist circumference and waist–hip ratio showed the effect of time and interaction of the effect of time with medication ($p < 0.001$ for the first 3 parameters; $p < 0.022$ for waist–hip ratio). Similar results for LOCF analysis ***Patients losing 5% of initial weight*** (ITT at all time points) C: 5/34 (14.7%); I: 26/35 (74.3%) ***Patients losing 5% of initial weight*** (LOCF at 6 months) C: 3/31 (9.7%); I: 26/34 (76.5%) ***Patients losing 10% of initial weight*** (ITT at all time points) C: 0/34 (0%); I: 19/35 (54.3%) ***Patients losing 10% of initial weight*** (LOCF at 6 months) C: 0/31 (0%); I: 19/34 (55.9%)	Participants were withdrawn if they became pregnant, presented with a concomitant severe disease, suffered from severe AEs, withdrew informed consent or failed to attend the clinic appointments 81 patients entered the trial ***Withdrawals prior to starting trial medication*** Move/job duties: 2 Pregnancy: 1 Severe type-2 diabetes with peripheral neuropathy: 1 Severe uncontrolled hypertension and arrhythmia: 1 Did not attend for initial tests: 6 Withdrew consent: 1 69 patients commenced DB treatment ***Withdrawals during DB treatment (C/I)*** Withdrew consent due to AEs: 0/3 Withdrew consent due to lack of efficacy: 17/7 Lost to F/U: 8/2 Wearing orthopaedic device: 0/1 ***Completers*** C: 9; I: 22 There were no differences in SBP between I and C at any time. I patients showed a small decrease during month 3 relative to baseline ($p < 0.05$)	***Study limitations, as noted by the study authors*** Possible unblinding due to AEs associated with sibutramine use ***Reviewer's comments*** ITT is defined as completers at 6 months for this trial; this is an unusual definition of ITT ***Sponsorship*** Quimica Knoll de Mexico, Mexico City, Mexico

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Cuellar *et al.*, 2000**[48]				The difference in the cumulative incidence of 5% and 10% loss of initial weight was statistically significant ($p < 0.001$) Patients in I reported decreased appetite, increased satiety and better adherence with diet from the first month of treatment onwards, and this remained constant up to the end of the trial. These effects were observed in C patients in the first 2 months for appetite and satiety, and during the first month for diet adherence. The I group had better scores considering each one of the months of treatment ***Mean weight loss at 6 months*** (in kg by ITT analysis) (95% CI) C: 0.9 (–0.8 to 2.8); I: 14.2 (11.5 to 17.2) ***Mean weight loss at 6 months*** (in kg by LOCF analysis) (95% CI) C: 1.3 (0.3 to 2.2); I: 10.4 (7.7 to 13.1) **% *Baseline weight remaining at 6 months*** (mean ± SD by ITT analysis) (95% CI) C: 98.7 ± 2.7 (100.4 to 96.9); I: 83.8 ± 7.6 (87.0 to 80.6) **% *Baseline weight remaining at 6 months*** (mean ± SD by LOCF analysis) (95% CI) C: 98.6 ± 2.7 (99.5 to 97.6); I: 88.2 ± 8.7 (91.1 to 85.2) ***Mean decrease in BMI at 6 months*** (in kg/m^2 by ITT analysis) (95% CI) C: 0.4 (–0.3 to 1.1); I: 5.6 (4.5 to 6.8) ***Mean decrease in BMI at 6 months*** (in kg/m^2 by LOCF analysis) (95% CI) C: 0.5 (0.1 to 0.9); I: 4.2 (3.1 to 5.2) ***Mean decrease in waist circumference at 6 months*** (in cm by ITT analysis) (95% CI) C: 1.8 (–0.8 to 4.4); I: 17.7 (14.6 to 20.8) ***Mean decrease in waist circumference at 6 months*** (in cm by LOCF analysis) (95% CI) C: 3.3 (1.4 to 5.1); I: 12.5 (9.2 to 15.8) ***Mean decrease in waist–hip ratio at 6 months*** (by ITT analysis) (95% CI) C: 0.01 (–0.05 to 0.03); I: 0.06 (0.04 to 0.08) ***Mean decrease in waist–hip ratio at 6 months*** (by LOCF analysis) (95% CI) C: 0.01 (–0.005 to 0.03); I: 0.04 (0.02 to 0.06)	There were no differences in DBP between I and C at any time. I patients showed a small decrease during months 2, 3, 4 and 5 of treatment relative to baseline ($p < 0.05$) 1 patient per group presented BP of > 140/90 mmHg. Both were patients with known hypertension, who failed to take the anti-hypertensive medication for several days. They became normotensive when medication was re-initiated There was a difference in HR between groups during month 1 ($p < 0.05$) (no further details given in paper). I patients showed a small increase during months 1, 2, 3 and 4 relative to baseline. 3 patients in I had tachycardia; all recovered without additional treatment ECG did not show significant variations between groups. Clinical laboratory tests did not show any abnormalities 23 patients in I reported 34 AEs and 16 patients in C reported 21 AEs. 3 patients in I withdrew consent due to AEs ***AEs (C/I)*** Upper respiratory tract infection: 2/6 Constipation: 2/6 Tachycardia: 0/3 Colitis: 0/2 Oedema of lower legs: 2/1 Hypotension: 2/0 Hypertension: 1/1 Headache: 1/1 Gastritis: 1/1 Other: 10/13	

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Fujioka *et al.*, 2000[47] ***Country*** USA ***Aim*** To determine the efficacy and tolerability of sibutramine in obese patients whose type-2 diabetes was poorly controlled on diet alone or with an oral antidiabetic agent ***Method of randomisation*** Method not stated; equal numbers randomised to treatment groups ***Outcomes*** Change in body weight; BMI; 5% and 10% body weight reduction relative to baseline; waist and hip circumferences; FPG; plasma insulin levels; serum lipids; blood chemistry; haematology; urinalysis; thyroid function; HbA_{1c}; BP; PR; ECG; QoL (assessed using SF-36[57] and Impact of Weight on Quality of Life questionnaire[58]); AEs ***Setting and length of treatment*** 16 medical centres in the USA; 5-week run-in period followed by 24-week DB treatment period	***Population*** Not stated ***Inclusion criteria*** *For run-in* Age at least 18 years; BMI 27–40 kg/m^2; diagnosis of type-2 diabetes mellitus, treated with diet alone or diet plus a single oral antidiabetic agent (a sulphonylurea or metformin) at a constant dose for at least 28 days prior to run-in; women were eligible if they had a negative serum pregnancy test, were at least 2 years postmenopausal, surgically sterilised or using a medically approved method of contraception *For DB phase* FPG 7.8–12.8 mmol/l and HbA_{1c} > 7% ***Exclusion criteria*** Use of insulin for more than 1 week within the 3 months prior to the run-in period or subsequently at any time prior to randomisation.	***5-week, SB, placebo run-in period for all patients*** Dietary counselling and nutrition plan to achieve minimum energy deficit of 250–500 kcal/day. Placebo once daily. Number of patients entering run-in not stated ***Standard care for all patients during DB study*** Dietary counselling and nutrition plan as above C: placebo once daily for 24 weeks (n = 86) I: sibutramine, initial dose 5 mg/day, titrated up to 20 mg/day by 5 mg increments every 2 weeks until week 6. The 20 mg/day dose was then continued until week 24 (n = 89)	***Gender*** (male/female) C: 42/44; I: 51/38 ***Age*** (mean ± SD in years) C: 55.0 ± 10.2; I: 53.5 ± 10.0 ***Ethnicity*** (caucasian/black/other) C: 63/16/7; I: 65/14/10 ***Weight*** (mean ± SD in kg) C: 98.2 ± 14.6; I: 99.3 ± 16.5 ***BMI*** (mean ± SD in kg/m^2) C: 33.8 ± 3.5; I: 34.1 ± 3.7 ***Waist/hip circumference*** (mean ± SD in cm) C: 110.0 ± 12.4/115.5 ± 11.2; I: 108.6 ± 10.2/114.7 ± 9.3 ***Number treated with diet only/diet + sulphonylurea/diet + metformin*** C: 12/60/14; I: 18/58/13 ***SBP/DBP*** (mean ± SD in mmHg) C: 128 ± 15/79 ± 7 I: 128 ± 14/79 ± 8 ***History of hypertension*** C: 37%; I: 39% ***% Patients using angiotensin-converting enzyme inhibitors/ calcium channel blockers/ α-adrenergic blockers/ diuretics*** C: 23%/13%/5%/12% I: 16%/16%/1%/9%	***Statistical techniques*** Analyses carried out for completers and according to LOCF. 2-way ANOVA used to analyse change from baseline for all patients for the LOCF dataset. 5% and 10% responder analyses and completer analyses performed using the Kruskal–Wallis test. Chi-squared test used to compare frequencies of patients achieving categorical reductions in HbA_{1c}. A linear regressions model with % change in body weight as the dependent variable and change in either HbA_{1c} or FPG as the independent variable was generated per treatment group By the first post-baseline visit (week 2) weight loss was significantly greater in I compared to C; this continued to week 24 and was generally similar in the LOCF and completers' datasets. Over all post-baseline visits, the % baseline weight lost was significantly greater in I compared with C (p < 0.001 for LOCF analysis and p < 0.001 for completers' analysis) **Results at 24 weeks:** ***5% loss of initial weight*** (by LOCF analysis) C: 1.2%; I: 27% p < 0.001 ***10% loss of initial weight*** (by LOCF analysis) C: 1.2%; I: 6% ns ***Weight gain at week 24*** (by LOCF analysis) C: 30%; I: 3.4% ***Mean weight change for all patients*** (by LOCF analysis) C: –0.4 kg (–0.5%) (n = 84) I: –3.7 kg (–3.8%) (n = 82) $p \leq 0.05$	***Withdrawals during DB trial*** C: 25/86 (29%); I: 29/89 (33%) ***Reasons for withdrawal during DB trial (C/I)*** AEs: 10/9 Lost to F/U: 1/0 Protocol deviation: 9/7 Failure to follow appointment schedule: 0/3 Other: 5/10 ***Number of AEs reported*** C: 275 events reported by 68 patients I: 250 events reported by 70 patients The authors state that the majority of AEs were mild or moderate in severity; 15 events were considered severe ***SAEs*** C: 1 patient; I: 5 patients The investigator judged the relationship to study drug as 'possible' in 1 of the 5 1 patients and as 'none' in the other 4. One I patient discontinued treatment due to a SAE that was judged by the investigator to be unrelated to the study medication. 3 patients in I discontinued treatment as a result of possible treatment-related AEs (dizziness, hyperglycaemia and nausea) that were mild to moderate in intensity	***Study limitations, as noted by the study authors*** In this study, calorie restriction was moderate (energy deficit 250–500 kcal/day). Greater weight losses in both study groups might have been observed had recommendations for calorie restriction been of greater magnitude ***Sponsorship*** Knoll Pharmaceutical Company, Mount Olive, NJ, USA

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Fujioka *et al.*, 2000**[47]	Use of other weight loss products, systemic β-adrenergic blockers, antidepressants, or monoamine oxidase inhibitors; history of marked diabetic complications, significant history of cardiovascular disease; PR > 90 bpm, SBP > 160 mmHg, DBP > 90 mmHg during study visits prior to randomisation		***Use of HMGCo-A-reductase inhibitor or a fibrate*** C: 10%; I: 14% ***PR*** (mean ± SD in bpm) C: 72 ± 9; I: 71 ± 8 ***FPG*** (mean ± SD in mmol/l) C: 9.9 ± 2.3; I: 10.2 ± 1.9 ***HbA_{1c}*** (mean ± SD as %) C: 8.3 ± 1.2; I: 8.4 ± 1.0 ***Fasting insulin*** (mean ± SD in pmol/l) C: 116 ± 64; I: 122 ± 62 ***Triglyceride*** (mean ± SD in mmol/l) C: 2.21 ± 1.29; I: 2.42 ± 1.51 ***Cholesterol*** (mean ± SD in mmol/l) C: 5.38 ± 1.03; I: 5.43 ± 0.93 ***HDL-C/LDL-C*** (mean ± SD in mmol/l) C: 1.08 ± 0.24/3.36 ± 0.80 I: 1.11 ± 0.32/3.34 ± 0.80	***Mean weight change for all patients*** (for completers) C: –0.3 kg (–0.4%) (n = 61) I: –4.3 kg (–4.5%) (n = 60) $p \leq 0.05$ ***Mean weight change in patients treated by diet alone*** (by LOCF analysis) C: –0.5 kg (–0.4%) (n = 12) I: –2.6 kg (–2.5%) (n = 18) $p \leq 0.05$ ***Mean weight change in patients treated by diet alone*** (for completers) C: –0.4 kg (–0.3%) (n = 11) I: –3.8 kg (–3.9%) (n = 8) $p \leq 0.05$ ***Mean weight change in patients treated by diet + sulphonylurea*** (by LOCF analysis) C: –0.4 kg (–0.4%) (n = 58) I: –3.6 kg (–4.0%) (n = 52) $p \leq 0.05$ ***Mean weight change in patients treated by diet + sulphonylurea*** (for completers) C: –0.3 kg (–0.3%) (n = 38) I: –4.0 kg (–4.4%) (n = 42) $p \leq 0.05$ ***Mean weight change in patients treated by diet + metformin*** (by LOCF analysis) C: –5.0 kg (–0.7%) (n = 14) I: –5.3 kg (–5.0%) (n = 13) $p \leq 0.05$ ***Mean weight change in patients treated by diet + metformin*** (for completers) C: –3.0 kg (–0.5%) (n = 12) I: –5.8 kg (–5.3%) (n = 10) $p \leq 0.05$	***AEs reported by more than 10% of patients in either treatment group*** (C/I) Infection: 21/23 Pain: 11/7 Sinusitis: 10/3 Back pain: 9/4 Constipation: 5/9 ***Vital signs*** Both groups showed small increases in supine SBP and DBP that were not significantly different. I showed a modest but statistically significant increase in PR compared with C ($p < 0.001$ for LOCF and completers). Postural changes of SBP, DBP and PR did not differ significantly between groups ***Withdrawals due to hypertension*** C: 2; I: 1 No patients were withdrawn due to tachycardia During DB treatment, I showed small numeric increases from baseline values in SBP (1–2 mmHg) and DBP (1–3 mmHg) compared with C. I showed modest statistically significant increases in PR compared with C, which ranged from 4.0 to 5.9 bpm for LOCF analysis ($p \leq 0.001$) and 2.9 to 7.0 bpm for completers ($p < 0.04$)	

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(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Fujioka *et al.*, 2000**[47]				***Change in BMI*** (mean ± SD in kg/m^2 by LOCF analysis) C: –0.2 ± 0.9; I: –1.3 ± 1.2 $p < 0.001$ ***Change in waist circumference*** (mean ± SD in cm) C: –2.0 ± 4.6; I: –3.4 ± 6.2 ns ***Change in hip circumference*** (mean ± SD in cm) C: –0.7 ± 6.1; I: –3.0 ± 5.6 $p = 0.01$ Unclear whether analyses of waist/hip circumference are LOCF or completers ***Glycaemic control*** In C, changes in HbA_{1c} and FPG were not significantly correlated with % change in body weight. In I, changes in HbA_{1c} and FPG were statistically significantly correlated with % change in body weight, indicating that weight loss with sibutramine was associated with improvement in glycaemic control ($p = 0.001$ and $p = 0.0064$, respectively). The largest improvement in HbA_{1c} was found in sibutramine-treated patients who sustained at least 10% weight loss, and was significant in both LOCF and completers' analyses ($p \leq 0.05$) in which the mean treatment differences when compared with all patients in C were –1.67% and –1.65%, respectively. The 5% responders in I also showed improved HbA_{1c}, but the differences relative to all patients in C were not statistically significant (–0.47% LOCF, –0.53% completers) Compared with all patients in C, both 5% and 10% responders in I showed statistically significant improvements in FPG ($p \leq 0.05$ for LOCF and completers). Fasting plasma insulin was also significantly improved in both the all-sibutramine group and 5% responders ($p \leq 0.05$ for LOCF and completers) Glycaemic control improved early in the course of DB treatment in I patients and was more marked in those who ultimately lost at least 5% of baseline weight. For 5% responders, changes in HbA_{1c} were significant at weeks 8 and 20 (mean treatment difference relative to placebo –0.42% and –0.51%, respectively). For 10% responders, change in HbA_{1c} was significant at week 20 (mean treatment difference –1.31%, $p < 0.02$). Similar results were seen for completers. Improvements in FPG in sibutramine-treated patients were also seen early in treatment and were more robust and durable in those who ultimately lost at least 5%	In general, patients who lost weight tended to show smaller increases in BP and PR. In 1 5% responders, SBP and DBP decreased relative to all patients in C. The mean increase in PR remained significantly greater in 5% responders (6.7 ± 10.9 bpm, $p = 0.007$ for LOCF; 6.9 ± 11.3 bpm, $p = 0.004$ for completers). However, the mean change in PR for 10% responders (4.4 ± 12.8 bpm) was not significantly different from that observed in all patients in C. Mean PR at each visit for all groups and analyses was 80 bpm maximum ***Laboratory, physical examination and ECG findings*** Haematology, chemistry, urinalysis, thyroid function, anti-nuclear antibody and physical examination data showed no changes consistent with a detrimental treatment effect. HR changes were statistically greater ($p < 0.001$) in I compared with C in ECGs done at weeks 12 and 24, consistent with changes seen in PR	

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Fujioka *et al*., 2000**[47]				***Change in HbA_{1c} (%) in all patients*** (mean ± SD by LOCF) C: 0.27 ± 0.94 (*n* = 82); I: 0.17 ± 0.99 (*n* = 80) ns ***Change in HbA_{1c} (%) in all patients*** (mean ± SD for completers) C: 0.25 ± 0.86 (*n* = 61); I: 0.06 ± 0.96 (*n* = 59) ns ***Change in FPG in all patients*** (mean ± SD mmol/l by LOCF analysis) C: 1.0 ± 2.1 (*n* = 84); I: 0.6 ± 2.5 (*n* = 82) ns ***Change in FPG in all patients*** (mean ± SD mmol/l for completers) C: 0.9 ± 2.1 (*n* = 61); I: 0.4 ± 2.5 (*n* = 60) ns ***Change in fasting plasma insulin in all patients*** (in pmol/l by LOCF analysis) C: 1.0 ± 52 (*n* = 71); I: –11 ± 47 (*n* = 66) $p \leq 0.05$ ***Change in fasting plasma insulin in all patients*** (in pmol/l by mean ± SD for completers) C: –1 ± 54 (*n* = 60); I: –13 ± 43 (*n* = 58) $p \leq 0.05$ ***Changes in lipid levels*** I showed larger mean decreases in triglycerides, which were significant in 5% responders and all patients in I vs C ($p = 0.007$ and 0.004, respectively for LOCF; 0.001 and 0.005 for completers). I also showed larger increases in HDL-C (ns) ***QoL assessments*** I showed favourable changes from baseline for all 8 scales of the SF-36[57] vs C. For I patients, significant improvements were found for general health at week 24 ($p \leq 0.05$ for LOCF). 5% responders showed significant improvements in health compared with 1 year ago at week 24 ($p \leq 0.05$ for LOCF). 10% responders showed significant improvement in general health at week 24. I patients also showed improvements in scale scores of the Impact of Weight on Quality of Life questionnaire.[58] Compared with all C patients, significant improvements were seen in the health scale at week 24 for 5% responders and I patients ($p \leq 0.05$, LOCF and completers)		

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Bray *et al.*, 1999[41] ***Country*** USA ***Aim*** To determine the effect of sibutramine on body weight of patients with obesity ***Method of randomisation*** Computer-generated list ***Outcomes*** Change in body weight; waist and hip circumference; vital signs; supine BP; PR; ECG; haematology; blood chemistry; urinanalysis; lipid levels ***Setting and length of treatment*** 7 centres in the USA; 2-week run-in followed by 24-week DB study	***Population*** Not stated ***Inclusion criteria*** Age 18–65 years; BMI 30–40 kg/m^2; women of childbearing potential were eligible if using adequate contraception ***Exclusion criteria*** Pregnancy; lactation; hypertension; cardiovascular disease; diabetes mellitus; haematological, pulmonary, hepatic, renal or immunological disease; diagnosis of major depression, panic disorder, anorexia nervosa, bulimia nervosa or other significant Axis I or Axis II psychiatric or neurological disorder; history of substance abuse within last 2 years; positive screen for illicit drugs or phenylpropanolamine; use of appetite- or weight-modifying medication within 14 days prior to screening; regular use of laxatives; treatment with	***2-week, SB, placebo run-in period for all patients*** Seen once by dietician for counselling. No other details given (n = 1047) ***Standard care for all patients during DB study*** Exercise programme of walking 20–30 minutes daily; instruction given in behavioural change techniques; women and men received instructions for energy intake of 1200 kcal/day or 1500 kcal/day respectively C: placebo, once daily, in the morning, for 24 weeks (n = 148) I1: sibutramine 1 mg, once daily, in the morning, for 24 weeks (n = 149) I2: sibutramine 5 mg, once daily, in the morning, for 24 weeks (n = 151) I3: sibutramine 10 mg, once daily, in the morning, for 24 weeks (n = 150)	***Gender*** (male/female) C: 27/121; I1: 28/121; I2: 30/121; I3: 32/118; I4: 25/127; I5: 35/111; I6: 28/123 ***Age*** (mean ± SD in years) C: 43.7 ± 8.60 I1: 44.5 ± 9.17 I2: 43.4 ± 8.72 I3: 43.3 ± 9.03 I4: 44.2 ± 10.20 I5: 42.9 ± 8.94 I6: 43.4 ± 8.95 ***Race*** (Caucasian/African American/Mexican American/other) C: 115/26/7/0 I1: 120/20/8/1 I2: 113/24/14/0 I3: 118/20/12/0 I4: 119/20/12/1 I5: 111/22/13/0 I6: 114/24/13/0 ***Weight*** (mean ± SD in kg) C: 97.1 ± 13.01 I1: 94.6 ± 13.22 I2: 95.7 ± 13.85 I3: 94.0 ± 14.44 I4: 93.7 ± 12.48 I5: 96.1 ± 14.34 I6: 95.8 ± 12.82 ***BMI*** (mean ± SD in kg/m^2) C: 34.9 ± 2.99 I1: 34.0 ± 2.93 I2: 34.8 ± 2.92 I3: 34.2 ± 2.90 I4: 34.3 ± 2.88 I5: 34.6 ± 3.05 I6: 34.9 ± 3.03	***Statistical techniques*** Completers were used for analyses of efficacy. In cases of dose reduction, efficacy data were analysed using the dose to which the patient was randomised. For safety analyses, all observed data were evaluated. Continuous variables analysed with ANOVA and rank ANOVA, with factors for centre, treatment and centre-by-treatment interactions. When the centre-by-treatment interaction was not statistically significant, the interaction term was removed from the model. Categorical variables analysed using chi-square tests, and pairwise comparisons vs placebo performed using Fisher's exact test ***Average weight loss during run-in*** 0.8 ± 1.5 kg Weight loss as % baseline weight for completers was dose-related and statistically significant vs placebo across all time points for the sibutramine 5 mg through 30 mg treatment groups (p < 0.05) ***Mean % changes in weight from baseline to week 24*** (for completers/LOCF analysis) C: –1.2/–0.9; I1: –2.7/–1.9; I2: –3.9/–3.1; I3: –6.1/–4.7; I4: –7.4/–5.8; I5: –8.8/–6.6; I6: –9.4/–7.7 ***Mean weight loss from baseline at 24 weeks*** (in kg for completers) C: 1.3; I1: 2.4; I2: 3.7; I3: 5.7; I4: 7.0; I5: 8.2; I6: 9.0 ***Patients losing ≥ 5% of baseline weight after 24 weeks*** C: 19.5%; I1: 25.3%; I2: 37.4%; I3: 59.6%; I4: 67.3%; I5: 71.9%; I6: 77.2% p < 0.01 for C vs I2, p < 0.001 for C vs I3, C vs I4, C vs I5, C vs I6	Patients who experienced either an intolerable AE, or a supine PR > 100 bpm at a single visit, or SBP > 160 mmHg, or DBP > 95 mmHg at a single visit were dose-reduced or withdrawn. Only 1 dose reduction was allowed for each patient ***Protocol for dose reduction*** Randomised / Reduced C: 0 mg / 0 mg I1: 1 mg / 0 mg I2: 5 mg / 0 mg I3: 10 mg / 5 mg I4: 15 mg / 10 mg I5: 20 mg / 10 mg I6: 30 mg / 15 mg ***Completers*** C: 87/148 (59%) I1: 95/149 (64%) I2: 107/151 (71%) I3: 99/150 (66%) I4: 98/152 (64%) I5: 96/146 (66%) I6: 101/151 (67%) Total: 683/1047 (65%) ***Completed + 6 weeks of F/U*** C: 53/148 (36%) I1: 61/149 (41%) I2: 59/151 (39%) I3: 60/150 (40%) I4: 50/152 (33%) I5: 60/146 (41%) I6: 56/151 (37%) Total: 399/1047 (38%)	***Study limitations, as noted by the study authors*** None stated ***Sponsorship*** Knoll Pharmaceutical Company, NJ, USA

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Bray *et al.*, 1999**[41]	psychotropic agents, benzodiazepines, oral hypoglycaemics, anti-hypertensive agents or anticholinergics	I4: sibutramine 15 mg, once daily, in the morning, for 24 weeks (n = 152) I5: sibutramine 20 mg, once daily, in the morning, for 24 weeks (n = 146) I6: sibutramine 30 mg, once daily, in the morning, for 24 weeks (n = 151) Week 24 was followed by a 6-week placebo washout period for all patients	Statistically significant (but not clinically significant) difference in BMI ($p < 0.05$) There were no significant differences between groups for waist circumference, hip circumference, family income, personal or family history of obesity, previous attempts at weight loss, or loss of weight during the run-in period	***Patients losing ≥ 10% of baseline weight after 24 weeks*** C: 0.0%; I1: 10.5%; I2: 12.1%; I3: 17.2%; I4: 34.7%; I5: 38.5%; I6: 45.5% $p < 0.01$ for C vs I1, $p < 0.001$ for C vs I2, C vs I3, C vs I4, C vs I5, C vs I6 Weight loss was most rapid during the first 12 weeks. The higher dose groups (10–30 mg) continued to lose weight throughout the study period, whereas the placebo and lower dose groups (1 and 5 mg) lost weight during the first 12 weeks and stabilised thereafter. When treatment was discontinued patients regained weight, with those losing the most regaining the most Waist and hip circumferences decreased significantly ($p < 0.05$, Dunnett's test) compared with placebo for the 10–30 mg sibutramine groups (data not shown in paper) ***Predictors of weight loss*** Patients losing 1.8 kg or more in the first 4 weeks of treatment were more likely to achieve a weight loss of 5% or more compared with placebo at 24 weeks ***Metabolic risk factors*** Statistically significant changes in serum lipids and uric acid were observed in patients losing weight on sibutramine; HDL-C increased, and total cholesterol, LDL-C, triglycerides and uric acid decreased For a given amount of weight loss, changes in lipids were similar whether weight loss was achieved on placebo or sibutramine. Because the weight loss achieved with sibutramine was greater vs placebo, the observed lipid changes were correspondingly greater. Fasting serum glucose also declined in patients who lost weight on sibutramine	***Dose reduction (includes patients who later withdrew)*** C: 9/148 (6%) I1: 10/149 (7%) I2: 14/151 (9%) I3: 18/150 (12%) I4: 20/152 (13%) I5: 33/146 (23%) I6: 44/151 (29%) Total: 148/1047 (14%) ***Withdrawals due to AE/lack of efficacy/other reason (%)*** C: 8/7/26; I1: 11/7/17; I2: 5/5/18; I3: 9/1/24; I4: 11/2/22; I5: 13/3/19; I6: 18/1/14 Total: 11/4/20 The following AEs prompted dose reductions: asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash and dyspnoea 'Other' reasons for withdrawal include lost to F/U, protocol violation and unknown **% *Patients reporting AEs*** (C/I1/I2/I3/I4/I5/I6) Dry mouth: 5.5/6.0/11.8/16.7/25.5/32.2/31.8 Anorexia: 12.2/20.1/18.9/18.7/21.4/32.2/31.8 Insomnia: 5.5/12.1/8.3/9.4/10.2/10.3/24.5 Appetite increase: 8.3/11.4/16.6/16.7/14.3/11.6/21.2	

continued

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Bray *et al.*, 1999**[41]				***Change from baseline in SBP (mmHg), DBP (mmHg) and PR (bpm) at week 24*** C: –0.8/1.7/0.6; I1: 0.3/1.2/0.3; I2: 2.1/2.5/3.3; I3: 2.8/4.2/6.0*; I4: 2.7/3.4/6.1*; I5: 4.0/5.0*/7.0*; I6: 3.3/4.1/5.3* *$p < 0.05$ vs C Other than changes in HR, no clinically or statistically significant changes in ECG intervals or arrhythmic events were observed. Data from physical examinations and laboratory tests showed no discernible treatment-related differences for any body system	Nausea: 4.4/3.4/4.1/3.4/5.1/8.2/12.6 Dyspepsia: 6.6/4.0/4.1/4.4/8.2/5.5/12.6 Nervousness: 5.5/4.7/5.3/6.4/7.7/12.3/11.3 Asthenia: 5.0/2.7/7.1/7.9/6.1/8.9/10.6 Dizziness: 3.3/4.7/8.9/7.9/8.2/12.3/7.9 Constipation: 4.4/6.7/13.0/10.8/11.7/12.3/7.9 Rash: 2.2/5.4/4.1/4.9/7.1/4.1/7.3 Palpitations: 0.6/2.0/0/4.9/2.6/4.1/6.0 Vasodilation: 0/1.3/2.4/2.0/2.0/4.8/5.3 Dyspnoea: 0/1.3/0.6/1.5/1.0/1.4/4.6 Taste perversion: 0.6/0.7/1.2/2.0/2.6/4.1/4.6 Hypertension: 2.2/2.0/1.2/4.9/5.1/1.4/3.3 Sweating: 0/0/1.2/1.0/2.6/4.1/2.6 Tachycardia: 1.1/0.7/1.8/4.4/7.7/6.8/2.6 Ecchymosis: 0/0/1.2/0.5/3.1/1.4/2.0 Paresthesia: 0/2.0/2.4/3.9/2.0/3.4/1.3	

(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Apfelbaum *et al.*, 1999[46] ***Country*** France ***Aim*** To determine the efficacy of long-term treatment with sibutramine in maintaining or improving weight loss in obese patients who had lost weight with a VLCD ***Method of randomisation*** Method not stated; assigned in blocks of 4 ***Outcomes*** Change in body weight; waist circumference; haematology; blood chemistry; urinalysis; BP; HR; ECG; adherence with dietary regimen (assessed with VAS); adherence with drug regimen (assessed by counting returned capsules); AEs ***Setting and length of treatment*** France, no other details given; 1-week run-in for screening tests followed by 4 (± 1) week VLCD followed by 12-month DB study for weight maintenance	***Population*** Patients were recruited from 12 medical centres in France that had a special interest in obesity or endocrinology ***Inclusion criteria*** *For VLCD* Outpatients; age 18–55 years; BMI > 30 kg/m^2 *For DB maintenance study* Weight loss of at least 6 kg at the end of the VLCD; still fulfilling initial criteria ***Exclusion criteria*** Obesity of endocrine origin; type-1 diabetes; type-2 diabetes treated with insulin or poorly controlled; supine DBP > 100 mmHg; medical illness; ECG or laboratory abnormalities; unsuccessful use of VLCD in the previous 6 months; more than borderline depression on the Clinical Global Impression scale; use of other therapies that could alter body weight or interfere with study medication	***1-week run-in period for all patients*** For screening only ***VLCD for all patients*** Prescription of 4 (± 1) week, site-specific, VLCD (220–800 kcal/day) ***Standard care for all patients during DB study*** The VLCD was discontinued. All patients resumed meals and received dietary counselling to decrease total calorie intake by 20–30% compared with their pre-VLCD intake. Patients were seen by a dietician every 3 months C: placebo once daily, in the morning, for 12 months (n = 78) I: sibutramine 10 mg once daily, in the morning, for 12 months (n = 82)	***Gender*** (male/female) C: 18/60 I: 15/67 ***Age*** (mean ± SD in years) C: 39.1 ± 9.1 I: 36.3 ± 9.5 ***Weight pre-VLCD*** (mean ± SD in kg) C: 105.1 ± 20.3 I: 103.4 ± 17.5 ***BMI pre-VLCD*** (mean ± SD in kg/m^2) C: 38.7 ± 6.8 I: 37.9 ± 5.9 ***Weight at randomisation*** (mean ± SD in kg) C: 97.7 ± 19.7 I: 95.7 ± 16.9 ***BMI at randomisation*** (kg/m^2) C: 35.9 ± 6.6 I: 35.1 ± 5.8 ***Weight loss on VLCD*** (kg) C: 7.4 ± 1.8 I: 7.7 ± 1.9	***Statistical techniques*** For both absolute and % changes in body weight after completion of the VLCD, ANOVA was performed at each time point with factors for treatment group, centre and the treatment-group-by-centre interaction. ITT analysis used LOCF. Proportions compared with chi-squared test. Changes from baseline for other variables were assessed using ANOVA ***Weight change from randomisation to 12 months*** (mean ± SD in kg) C: +0.5 ± 5.7; I: –5.2 ± 7.5 p = 0.004 Significantly greater weight loss occurred in I than C at each monthly assessment (p < 0.05) ***At least 5% loss of baseline weight at 12 months*** (by ITT analysis) C: 55%; I: 86% p < 0.001 ***At least 10% loss of baseline weight at 12 months*** (by ITT analysis) C: 23%; I: 54% p < 0.001 ***20% or more loss of baseline weight at 12 months*** (by ITT analysis) C: 3%; I: 17% p < 0.01 ***Maintenance of ≥ 25% weight loss following VLCD at 12 months*** (by ITT analysis) C: 83%; I: 96% p < 0.01 ***Maintenance of ≥ 50% weight loss following VLCD at 12 months*** (by ITT analysis) C: 76%; I: 93% p < 0.01	45/205 withdrawals during VLCD ITT analysis included 159 patients (one patient in I did not provide a post-baseline assessment of body weight) ***Withdrawals during DB phase*** AEs: C = 5; I = 2 Lack of efficacy: C = 6; I = 1 Other reasons: C = 19; I = 19 Total: C = 30; I = 22 Of 108 patients who completed the study, 9 (3 in C and 6 in I) were excluded from the completers' analysis because their 12-month assessment was performed more than 6 days after the last dose of trial medication ***Number (%) of patients reporting an AE*** C: 63/78 (81%); I: 72/82 (88%) ***Number of AEs reported*** C: 309; I: 331 ***Most common reported AEs*** (no. of patients reporting) Pharyngitis: C = 18; I = 17 Constipation: C = 4; I = 15 Headache: C = 10; I = 13 Bronchitis: C = 9; I = 12 Back pain: C = 9; I = 11 Anxiety: C = 5; I = 9 Asthenia: C = 8; I = 9 Flu syndrome: C = 8; I = 9 Insomnia: C = 7; I = 9	***Study limitations, as noted by the study authors*** None stated ***Sponsorship*** Sponsorship of trial not stated, but study medications provided by Knoll Pharmaceuticals

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(A) For published RCTs *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Apfelbaum *et al.*, 1999[46]**				***Maintenance of ≥ 100% weight loss following VLCD at 12 months*** (by ITT analysis) C: 41%; I: 74% $p < 0.001$ Similar results were seen for completers' analysis ***Change in waist circumference at 12 months*** (mean ± SD in cm) C: –1 ± 7; I: –6 ± 8 $p < 0.001$ ***Weight regain 3 months after treatment cessation*** (mean ± SD in kg) C: 2.3 ± 2.9; I: 4.3 ± 3.1 $p = 0.009$ From baseline to endpoint, triglyceride levels were reduced and HDL-C levels were increased in I compared with C ($p < 0.05$). No other between-group differences in lipid levels were noted. LDL-C levels increased in both groups from baseline levels when patients received the VLCD Adherence with the drug regimen was more than 97% in both groups. There were no significant differences between groups for patient's self-reported ease in adhering to dietary advice	Nausea: C = 3; I = 9 Dry mouth: C = 4; I = 8 $p = 0.01$ for constipation ***Withdrawals due to AEs*** C: 5 (2 pregnancies, 1 chest tightness, 1 development of hypertension, 1 headache, insomnia and dizziness) I: 2 (1 anxiety, 1 depression) Laboratory variables, other than uric acid, which declined more in I, showed no clinically or statistically significant changes in either group There were no statistically significant changes between groups in SBP. At 6 months, there was a significant between-group difference for the change from baseline in DBP C: –1.9 ± 2.2 mmHg I: +1.5 ± 2.0 mmHg $p < 0.05$ PR increased significantly at all time points in I compared with C ($p < 0.05$). HR (from ECG) increased in both groups. The mean difference between C (+1 ± 9 bpm) and I (+8 ± 11 bpm) was statistically significant at 6 months only ($p < 0.001$). No other clinically important ECG changes were noted	

(B) For RCTs from the manufacturer

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Wirth, 1998[49] ***Country*** Germany ***Aim*** To demonstrate that weight loss in obese patients on continuous treatment with sibutramine 15 mg over a period of 48 weeks is equivalent to that in obese patients receiving sibutramine 15 mg at intervals over the same period of time ***Method of randomisation*** Not stated ***Outcomes*** *Efficacy* Primary outcome: weight loss in kg Secondary outcomes: BMI; waist–hip ratio *Safety* BP, HR, laboratory tests and adverse drug reactions ***Setting and length of treatment*** Multicentre; 48 weeks	***Population*** Not stated ***Inclusion criteria*** *For 4-week run-in phase* Ambulatory, obese patients with a BMI between ≥ 30 and ≤ 40 kg/m^2 *For DB phase* Only patients that lost ≥ 2 kg or ≥ 2% of their screening body weight were randomised to the 44-week DB phase	***4-week, open-label treatment period with sibutramine 15 mg for all participants*** *Standard care for all patients during DB study* General dietary advice concerning healthy eating and calorie reduction C: sibutramine 15 mg orally, once daily, for 4 weeks; placebo given once daily for 44 weeks (*n* = 201/ PP population: *n* = 137) I1: sibutramine 15 mg orally, once daily, given for a total of 48 weeks in 12-week blocks separated by 6-week intervals on placebo therapy (*n* = 395/ PP population: *n* = 303) I2: sibutramine 15 mg orally, once daily for 48 weeks (*n* = 405/ PP population: *n* = 312)	Not reported	***Statistical techniques*** Efficacy was assessed in the PP population. Therapeutic effects in the treated group were demonstrated by *t* tests at the α = 0.05 level. The safety and tolerability assessment was based on the ITT population. In the statistical analysis, a descriptive assessment of the efficacy and safety was also made in subgroups The LOCF method for the primary study parameter was used for the ITT population, whereas only the observed cases were used for the PP population. 3 standards were used in the assessment: descriptive statistics, incidences and individual lists All AEs in each group were listed. AEs that occurred in the run-in phase were included in the treated group comparison if they persisted in the DB treatment phase and became more severe (treatment-emergent signs and symptoms = TESS) The laboratory results are presented in shift tables based on the normal ranges. All laboratory parameters were also presented descriptively ***Mean weight change*** (kg for PP population) C: 0.2; I1: –3.9; I2: –4.4 ***Mean weight change*** (kg for ITT population) C: –3.8; I2: –7.9 ***Mean change in waist circumference from screening*** (in cm by LOCF analysis (no. of patients)) C: –4.1 (175); I2: –7.8 (376) Weight loss in women in all treated groups was more pronounced than in men. With a *p*-value of the combined *t* test method of 0.0213 and a 95% CI, –1.296 to 0.449, which lies within the equivalence range of –1.5 to 1.5, the null hypothesis can be rejected Comparison of the weight changes of –4.4 kg on continuous treatment and 0.2 kg on placebo reveals that the second null hypothesis regarding the equivalence between continued and placebo therapy with a *p*-value of 0.0001 and a CI of –5.68 to –3.14, which does not contain a zero, can be rejected The third null hypothesis, with a *p* = 0.0001 and a CI with a lower limit of 2.65 and an upper limit of 5.32, assuming an equivalence between placebo and interval therapy, can be rejected On interval therapy the mean weight change was –3.92 kg and on placebo was 0.2 kg	***Number of patients completing*** C: 146/201 I1: not reported I2: 326/405	***Study limitations, as noted by the study authors*** None ***Reviewer's comments*** Most results only presented for PP population; some results for ITT but I1 not included ***Sponsorship*** Knoll Pharmaceuticals

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd ***Wirth, 1998***[49]			Not reported	Looking at the assessment of the weight differences between the phases, it was found that in the placebo phases between visits 4 and 5 and 7 and 8, patients receiving interval therapy gained 0.6 and 1 kg, respectively, whereas patients on continuous therapy lost –0.7 and –0.1 kg % ***Patients losing 5% of baseline body weight*** (for PP population) C: 40.9; I1: 69.6; I2: 69.9 % ***Patients losing 10% of baseline body weight*** (for PP population) C: 14.6; I1: 39.3; I2: 35.6 % ***Patients losing 5% of baseline body weight*** (for ITT population) C: 35.3; I2: 65.2 % ***Patients losing 10% of baseline body weight*** (for ITT population) C: 13.4; I2: 32.3 ***Safety*** In the run-in phase, AEs with a distribution pattern corresponding to that of the typical pharmacological effects of sibutramine occurred in only 25% of the patients After randomisation there was hardly any difference in the incidence of AEs in the treated groups, i.e. the mean incidence was 75% with slight advantages for the patients in the interval therapy group. This advantage in favour of the interval therapy group is even more marked if one regards the incidence of SAEs and discontinuations of treatment owing to AEs A total of 54 SAEs were reported in the course of the study and for up to 3 months after treatment (2 SAEs in the run-in phase, 30 SAEs under continuous therapy, 10 under interval therapy, 12 under placebo). However, a causal relationship with the study medication does not appear to be likely in most cases With regard to the clinically relevant laboratory data, only a slight decline in triglycerides and an increase in HDL were observed during the study in both sibutramine-treated groups ***Mean changes in triglycerides*** (mg/dl by ITT analysis) C: –11.0l; I2: –14.0 ***Mean changes in total cholesterol*** (mg/dl by ITT analysis) C: –2.0; I2: 1.0 ***Mean changes in LDL*** (mg/dl by ITT analysis) C: –6.0; I2: –3.0 ***Mean changes in HDL*** (mg/dl by ITT analysis) C: 4.0; I2: 9.0		

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Smith, 1994[50] ***Country*** UK ***Aim*** To assess the long-term efficacy and tolerability of sibutramine in the treatment of mild to moderate obesity To assess the long-term safety of sibutramine in mild to moderate obesity ***Method of randomisation*** Not stated ***Outcomes*** Weight; waist–hip ratio; visual analogue scales of hunger, appetite, craving for savoury, sweet and carbohydrate foods; satiety; snacking; dietary compliance; safety ***Setting and length of treatment*** 12 general practice centres in the UK; 12-month DB study	***Population*** Not stated ***Inclusion criteria*** Patients in general practice with BMI 27–40 kg/m^2	***2-week washout period for all patients*** Dietary advice was given before entry to the washout period ***Standard care for all patients during DB study*** Dietary advice was given throughout the study C: placebo, once daily, orally (n = 163) I1: sibutramine 10 mg, once daily, orally (n = 161) I2: sibutramine 15 mg, once daily, orally (n = 161)	Not reported	***Statistical techniques*** Kruskal–Wallis test; Wilcoxon rank sum test; repeated measures ANOVA; Satterthwaite's approximation; Greenhouse–Geisser method; ANOVA; 2-way analysis of ranks; Boos–Brownie test; Cochran–Mantel–Haenszel test; log-rank test; ANCOVA; chi-squared test; Fisher's exact test ***% Patients losing more than 5% of their baseline body weight*** (for completers) C: 29; I1: 56; I2: 65 $p < 0.01$ for I1 vs C; $p < 0.001$ for I2 vs C ***% Patients losing more than 10% of their baseline body weight*** (for completers) C: 8; I1: 30; I2: 39 $p < 0.01$ for I1 vs C; $p < 0.001$ for I2 vs C ***% Patients losing more than 5% of their baseline body weight*** (total n; transformed data) C: 20 (157); I1: 39 (154); I2: 57 (153) $p < 0.001$ for I1 vs C and for I2 vs C ***% Patients losing more than 10% of their baseline body weight*** (total n; transformed data) C: 7 (157); I1: 19 (154); I2: 34 (153) $p < 0.01$ for I1 vs C; $p < 0.001$ for I2 vs C ***% Patients losing more than 5.45 kg over the first 12 weeks*** (for completers) C: 11; I1: 37; I2: 56 $p < 0.001$ for I1 vs C and for I2 vs C ***Patients gaining weight*** (for completers) C: 28; I1: 15; I2: 13 ***Mean % weight loss*** (for completers) C: 1.9; I1: 5.5; I2: 7.2 $p < 0.001$ for I1 vs C and for I2 vs C ***Mean actual weight loss*** (in kg for completers) C: –1.8; I1: –4.8; I2: –6.1 $p < 0.01$ for I1 vs C; $p < 0.001$ for I2 vs C ***Mean actual weight loss*** (in kg for ITT LOCF analysis) C: –1.6; I1: –4.4; I2: –6.4 $p < 0.01$ for I1 vs C; $p < 0.001$ for I2 vs C ***Reduction in BMI*** (kg/m^2 for completers) C: –0.8; I1: –1.8; I2: –2.1 $p < 0.001$ for I1 vs C and for I2 vs C There were statistically significantly greater reductions from baseline to endpoint	A total of 256 patients completed the study: C = 80; I1 = 82; I2 = 94 62 patients were withdrawn due to AEs: C = 24; I1 = 18; I2 = 20 There were 30 SAEs The number of patients withdrawn because of lack of efficacy was greatest in the placebo group and decreased with increasing dose of sibutramine: C = 10; I1 = 5; I2 = 2 5 of the other reported serious or potentially SAEs resulted in withdrawal of the patient. These included septicaemic shock and excision of fibroid in the placebo group; 'drop attacks' and perforated diverticular disease requiring surgery in the sibutramine 10 mg group and frequent ventricular ectopics in the sibutramine 15 mg group. The remaining 13 serious or potentially SAEs that occurred during the study did not result in withdrawal	***Study limitations, as noted by the study authors*** None stated ***Reviewer's comments*** None ***Patients gaining weight*** (for completers) C: 28; I1: 15; I2: 13 ***Sponsorship*** Knoll Pharmaceuticals

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Smith, 1994**[50]				in waist–hip ratio for the sibutramine 10 mg and 15 mg groups (0.04 and 0.03, respectively) compared to placebo (0.01; $p < 0.01$), as well as greater reductions in waist and hip circumferences. There were some treatment-related trends, in favour of sibutramine, for the visual analogue eating scales averaged over time There was a small increase in weight after stopping treatment which was statistically significant (1.1 kg and 1.3 kg in the sibutramine 10 mg and 15 mg groups compared with 0.4 kg in the placebo group) The AEs most commonly reported by patients who received sibutramine were headache, infection, constipation, dry mouth and pharyngitis The proportion of patients in the sibutramine 15 mg group who reported AEs was statistically significantly higher than in the placebo group ($p < 0.0001$). Overall, 132 patients in the sibutramine 15 mg group (82%) reported 493 events, 122 patients in the sibutramine 10 mg group (76%) reported 385 events and 110 patients in the placebo group (67%) reported 289 events There were statistically significant differences between the sibutramine treatment groups and placebo. Those events reported in the Digestive and Nervous COSTART body systems were more likely to be related to sibutramine, particularly the number of patients reporting constipation or dry mouth. For the other COSTART body systems for which there was a statistically significant difference between the treatments (haemic and lymphatic and special senses), there was no specific event or group of events that explained these results; however, the total number of patients reporting events in these groups was small There were statistically significant reductions in triglycerides at month 6 for the sibutramine 10 mg and 15 mg treatment groups (18% and 19%, respectively) compared with placebo (3%) Uric acid levels were also statistically significantly reduced at month 6 for both sibutramine treatment groups (7%/7% for the 10/15 mg groups compared to 2% in the placebo group) and endpoint and final assessment for sibutramine 15 mg There were statistically significant increases in HR compared to placebo, with maximum increase at month 6 (4.5 and 5.8 bpm in the sibutramine 10 and 15 mg groups, respectively, from the ECG recordings; $p < 0.01$ for both). By the endpoint of the study, the increase in HR compared to placebo was smaller and only statistically significant in the sibutramine 15 mg group (2.8 bpm in the sibutramine 10 mg group and 4.9 bpm in the 15 mg group ($p < 0.01$) from the ECG recordings). Changes in absolute BP were small and were not clinically significant		

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Smith, 1994**[50]				Sibutramine-treated patients showed no evidence of increased depression symptoms after completion of treatment 62 patients were withdrawn due to AEs (24 in the placebo group, 18 in the 10 mg group and 20 in the 15 mg group). A total of 30 serious or potentially SAEs were reported during the study; 7 of these were hospitalisations for planned elective procedures and these patients were not withdrawn from the study. Most of the events were unremarkable and recorded as not related to study treatment There were 5 pregnancies during the study (3 in the placebo group and 2 in the sibutramine 15 mg group). 3 of these resulted in withdrawal of the patient from the study (2 in the placebo group and 1 in the sibutramine 15 mg group); normal deliveries were recorded for all of these patients. For the other 2 pregnancies, the one in the placebo group was diagnosed 4 weeks after the patient had been withdrawn. A termination was performed and the patient recovered. The other pregnancy was in the sibutramine 15 mg group and was diagnosed on completion of the study. It was estimated that the pregnancy had occurred about 2 months before the end of the study period. The patient gave birth at 35 weeks gestation and recovered. The baby was convulsing in the neonatal period and a tentative diagnosis of viral meningitis was made. The only abnormality on lumbar puncture was an increase in glucose; aerobes were grown from the amniotic liquor. The baby was discharged from hospital but was still receiving phenobarbitone. Although the baby was developing reasonably well physically, subsequent EEGs showed some growth abnormality and arrhythmias. The baby is still receiving anti-convulsant therapy and F/U will continue. Relationship to study therapy for the convulsions is unknown		

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
James, 1999[51] ***Country*** UK ***Aim*** To assess the effect of sibutramine combined with a diet and exercise programme on maintenance of weight loss and other outcomes ***Method of randomisation*** Not stated ***Outcomes*** *Efficacy* Changes in body weight, BMI, waist and hip circumferences, waist–hip ratio, body composition, dietary data, dietary adherence, physical activity, glucose, HbA_{1c}, insulin, C-peptide and serum lipid levels Successful weight maintenance was defined as maintaining at least 80% of weight lost during the run-in period at each time point *Safety* Changes in BP, PR, laboratory variables and AEs ***Setting and length of treatment*** 8 specialist obesity centres in Europe; 6-month open, run-in phase followed by an 18-month DB phase	***Population*** Not stated ***Inclusion criteria*** *For run-in* Hospital outpatients, of either sex, aged 18–65 years, with a BMI within the range 30–45 kg/m^2 *For DB phase* Patients had to lose at least 5% of baseline body weight during run-in to be eligible for the DB phase	***6-month, sibutramine 10 mg once-daily run-in period for all patients*** 605/499 patients entered/completed the open run-in phase ***Standard care for all patients during DB study*** 467 patients followed an individualised diet (600 kcal deficit) throughout the study; the energy content of the diet was based on each individual's energy expenditure. Exercise plan (based on basal metabolic rate measured at screening and months 3 and 6, adjusted to maintain weight lost in open phase) was provided throughout the study. Dietetic advice at 2- to 4-week intervals C: placebo once daily (n = 115) I: sibutramine 10 mg, 15 mg or 20 mg once daily (dose titrated according to weight change) (n = 352)	Not reported Patients had a mean ± SD weight loss of 11.9 ± 5.1 kg (n = 467) during 6-month open phase	***Statistical techniques*** 2-sample t test, log-rank test, logistic regression, Cox's proportional hazards model, Wilcoxon rank sum test, ANCOVA ***% Successful weight maintenance at 12/18/24 months*** C: 38%/23%/16%; I: 75%/62%/43% $p < 0.001$ ***% Successful weight maintenance at endpoint*** C: 14%; I: 41% $p < 0.001$ ***Adjusted mean change from baseline to endpoint for weight loss*** (kg) C: –4.9; I: –8.9 $p < 0.001$ ***Adjusted mean change from baseline to endpoint for waist circumference*** (cm) C: –4.8; I: –8.5 $p < 0.001$ Changes in waist and hip circumferences and waist–hip ratio followed the same pattern as the weight change profile Reductions in triglycerides and very-LDL-C levels that were achieved during the open 6-month run-in phase of the study were maintained in the sibutramine DB treatment group; patients who received placebo during the DB period showed statistically significant increases in these variables. Indicators of glycaemic control also showed overall improvements in sibutramine-treated patients from baseline (month 0) to endpoint with reductions in insulin and C-peptide together with a fall in fasting glucose. Small reductions in HbA_{1c} were evident and decreases in uric acid were noted	605 patients entered the 6-month open run-in phase 499 patients completed run-in 467 patients were eligible (lost > 5 kg) for 18 months DB 261 patients completed DB: C = 57; I = 204 54 patients withdrew during the DB study Data on 467 were analysed ***Safety results*** The most common AEs reported during sibutramine treatment were dry mouth, infection, headache, pharyngitis, constipation, flu syndrome, insomnia, nausea, back pain, increased appetite, accidental injury, rash, dizziness, sweating, abdominal pain, asthenia and arthralgia ***SAEs*** C: 4; I: 29 ***Withdrawals during DB study due to non-SAEs*** C: 6; I: 48 There were no changes of clinical concern in the safety laboratory variables	***Study limitations, as noted by the study authors*** Dose titration permitted to 15 mg and 20 mg to maintain weight lost in 6-month open phase ***Reviewer's comments*** No baseline data ***Sponsorship*** Knoll Pharmaceuticals

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **James, 1999**[51]				Sibutramine-treated patients who lost ≥ 10% or 15% of their run-in body weight maintained significantly more weight loss at endpoint than patients who lost < 10% or < 15% of their run-in body weight, irrespective of the treatment group they were randomised to for the DB period of the study. For the subgroup of patients who achieved successful weight maintenance there were further decreases in waist circumference, hip circumference and waist–hip ratio for the sibutramine DB treatment group; improvements in lipids and glycaemic parameters were maintained At endpoint, a larger proportion of patients who received sibutramine during the DB phase had lost ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% of their baseline (month 0) body weight compared with patients given placebo **% *Patients losing ≥ 5% of baseline weight at endpoint*** C: 56 (49%); I: 235 (67%) **% *Patients losing ≥ 10% of baseline weight at endpoint*** C: 22 (19%); I: 131 (37%) **% *Patients losing ≥ 15% of baseline weight at endpoint*** C: 6 (5%); I: 59 (17%) **% *Patients losing ≥ 20% of baseline weight at endpoint*** C: 3 (3%); I: 31 (9%)		

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Rissanen, 1998[52] ***Country*** Finland ***Aim*** To evaluate the effects of treatment with sibutramine compared with placebo, upon weight loss, and the effects of weight loss upon glycaemic control and QoL, in obese type-2 diabetic patients previously untreated with anti-diabetic medication. A further objective: to evaluate chronic effects over 3 years of treatment To determine the incidence of left-sided valvular heart disease in obese patients who had received sibutramine or placebo for periods of up to 16 months To evaluate the efficacy and safety of sibutramine treatment upon weight loss and maintenance, and QoL and weight loss effects upon glycaemic control in obese type-2 diabetic patients not previously treated with anti-diabetic medication and subject to hypocaloric (700 calories) dietary advice; ongoing study	***Population*** Obese type-2 diabetic patients previously untreated with anti-diabetic medication ***Inclusion criteria*** Type-2 diabetic patients (fasting glucose > 7.8 mmol/l in plasma or > 6.7 mmol/l in blood), untreated with recent or long-term anti-diabetic medications; obese with a BMI of ≥ 28 kg/m^2; and aged 25–70 years	***2-week, placebo run-in period for all patients*** 700 calorie-deficit diet ***Standard care for all patients during DB study*** *12 months* 700 calorie-deficit diet C: placebo orally, 1 capsule daily, before breakfast (*n* = 122) I: sibutramine 15 mg orally, 1 capsule daily, before breakfast (*n* = 114)	Not reported	***Statistical techniques*** Score test, Shapiro–Wilk, D'Agostino–Pearson, Levene's test; chi-squared test, 2-sample *t* test, ANCOVA, log-rank test, rank analysis of covariance, Hodges–Lehmann estimator, Wilcoxon rank-sum test, logistic regression **Adjusted mean changes from baseline in efficacy variables ITT data to month 12:** ***Actual body weight*** (kg) C: –2.7; I: –7.5 *p* < 0.001 The OR for a better outcome (i.e. greater weight loss) for ITT sibutramine 15 mg patients was 5.47 (95% CI, 3.29 to 9.11) compared to placebo (*p* < 0.001) ***Glycosylated haemoglobin*** (%) C: –0.2; I: –0.3 ns ***BMI*** (kg/m^2) C: –0.9; I: –2.7 *p* < 0.001 ***Waist circumference*** (cm) C: –3.3; I: –7.1 *p* < 0.001 ***Hip circumference*** (cm) C: 1.9; I: –4.7 *p* < 0.001 ***Waist–hip ratio*** (× 100) C: –1.3; I: –2.5 *p* < 0.05 **Median percentage change from baseline ITT data to month 12:** ***C-peptide*** (nmol/l) C: –11.7; I: –17.1 ns ***Fasting glucose*** (mmol/l) C: 0.0; I: –3.6 ns	***Numbers in ITT analysis*** (*n* = 232) C: 121; I: 111 ***Numbers completed 12 months*** C: 108; I: 102 ***PP completing 12 months*** C: 96; I: 89 In total, there were 9 sibutramine 15 mg patients who withdrew with AEs and 12 placebo patients *Amendment*: 24 patients withdrew before the start of the echo study and 1 patient did not fulfil entry criteria. In all, 211 patients were scheduled for the echo study and 210 completed by the cut-off date (12 months). Of the 210 patients, 149 were in the DB phase (72 sibutramine; 77 placebo) and 61 in the open phase (57 sibutramine 15 mg; 4 sibutramine 20 mg)	***Study limitations, as noted by the study authors*** None ***Reviewer's comments*** None ***Sponsorship*** Knoll Pharmaceuticals

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Rissanen, 1998**[52] ***Method of randomisation*** Not stated ***Outcomes*** *Primary efficacy variables* Body weight and glycosolated haemoglobin *Secondary efficacy variables* BMI, waist and hip circumferences, C-peptide, fasting glucose, cholesterol (total, and LDL and HDL), triglycerides, QoL survey, time to starting anti-diabetic medication, dietary adherence *Safety* Vital signs, AEs, laboratory variables, ECG data, echocardiographic data ***Setting and length of treatment*** Multicentre trial, 12 months DB and a further 24 months open				***Triglycerides*** C: 7.1; I: –11.3 $p < 0.001$ ***Total cholesterol*** C: 4.4; I: 4.0 ns ***HDL-C*** C: –3.5; I: 4.2 $p < 0.001$ ***LDL-C*** C: 6.6; I: 4.6 ns **% *Patients weight loss at endpoint of ≥ 5%*** C: 17%; I: 65% $p < 0.001$ **% *Patients weight loss at endpoint of ≥ 10%*** C: 5%; I: 27% $p < 0.001$ Diabetic status was not altered to a significant extent but favoured sibutramine for each parameter, as shown above for changes in fasting glucose, glycosolated haemoglobin and C-peptide. However, compared to the placebo patient group, those patients who achieved ≥ 5% and ≥ 10% body weight loss on sibutramine (65% and 27%, respectively; placebo 17% and 5%, respectively: $p < 0.001$ for both) had significant improvements in glycosolated haemoglobin (–0.3%; $p = 0.02$ and –0.5%; $p = 0.002$, respectively). For the change from baseline to endpoint in the QoL assessments, only 1 of 9 scales was significantly different between treatments, with improved reported heath transition for sibutramine 15 mg ($p = 0.006$). HDL-C increased and triglycerides decreased for sibutramine 15 mg compared to placebo ($p < 0.001$). There was no significant difference between the 2 groups in the time to starting anti-diabetic medication ($p = 0.72$). Dietary compliance at endpoint was moderately better in the sibutramine 15 mg than in the placebo group, but the difference was ns ($p = 0.053$)		

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Rissanen, 1998**[52]				***Safety results*** The sibutramine 15 mg and placebo groups did not differ significantly in the proportions of patients with AEs (84% and 90%, respectively), withdrawal from the study (11% in both groups), or withdrawal on account of AEs or death (8% and 10%, respectively). In the sibutramine 15 mg group compared to placebo, there were more cardiovascular events and nervous system events, and higher incidence of dry mouth, sweating, fungal skin infection, pharyngitis, accidental injury, asthenia, peripheral vascular disorder and eczema, each occurring in at least 5% of patients, with tachycardia in 4% compared to 1% of patients given placebo. A total of 19 specific events occurred at greater incidence in the placebo group. SAEs occurred at similar rates in the 2 treatment groups, with 13 in the sibutramine 15 mg group (including 1 death with a cerebral carcinoma) and 12 in the placebo group. In all, 6 were considered at least possibly related to therapy: 4 in the sibutramine 15 mg group (1 suspected cerebellar infarction leading to withdrawal, 2 cases of cholecystolithiasis and 1 case of palpitations with hyperventilation) and 2 in the placebo group (angina leading to withdrawal and haemicrania). In total, there were 9 sibutramine 15 mg patients who withdrew with AEs and 12 placebo patients. Of those that were not serious, 9 were thought at least possibly to relate to study therapy: 2 in the sibutramine 15 mg group (elevated liver enzymes and increased sweating) and 7 in the placebo group (2 cases of depression, 2 of insomnia, and 1 each of fatigue, vertigo and dyspepsia) For sibutramine 15 mg compared to placebo, there were larger reductions in uric acid, alanine and aspartate, and aminotransferases, greater increases for urea and platelets, and a reduction compared to an increase for total bilirubin. For vital signs, adjusted mean increases from baseline to endpoint were significantly greater for the sibutramine 15 mg group compared to placebo for PR ($p < 0.001$) and ECG HR ($p = 0.001$), but not for diastolic ($p = 0.06$) or systolic BP ($p = 0.81$)		

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
Williams, 1999[53] ***Country*** UK ***Aim*** To evaluate the effect of sibutramine treatment on weight reduction in obese type-2 diabetic patients stabilised with metformin and to evaluate the effect of that weight loss on metabolic control ***Method of randomisation*** Not stated ***Outcomes*** *Efficacy* Change in body weight and glycosolated haemoglobin (HbA_{1c}), changes in fasting glucose, insulin, C-peptide concentrations, dietary adherence and waist/hip circumference *Safety* AEs, laboratory investigations (haematology, biochemistry, urinalysis and pregnancy testing), ECG and vital signs (BP and PR) ***Setting and length of treatment*** Multicentre, multinational trial; 12 months	***Population*** Obese, type-2 diabetic patients stabilised with metformin ***Inclusion criteria*** Obese, type-2 diabetic patients (BMI ≥ 27 kg/m^2) aged 25–70 years, and treated with metformin for at least 3 months but not more than 2 years	***Standard care for all patients during DB study*** 195 patients followed a general dietary advice concerning healthy eating and calorie reduction C: placebo, once daily, orally (n = 64) I1: sibutramine 15 mg, once daily, orally (n = 69) I2: sibutramine 20 mg, once daily, orally (n = 62)	Not reported	***Statistical techniques*** Logistic regression, ANCOVA, 2-sample t test, Hodges–Lehmann estimator, proportional odds model, regression analysis and 1-way ANOVA, chi-squared test, regression analysis of slopes, Fisher's exact test, 1-sample t test **Efficacy results:** ***Mean change in body weight after 12 months*** (in kg by ITT analysis) C: –0.2; I1: –6.2; I2: –8.5 $p < 0.001$ for C vs I1 and C vs I2 ***Mean change in BMI after 12 months*** (in kg/m^2 by ITT analysis) C: –0.1; I1: –2.2; I2: –3.2 $p < 0.001$ for C vs I1 and C vs I2 ***Mean change in waist circumference after 12 months*** (in cm by ITT analysis) C: 0.0; I1: –5.6; I2: –7.2 $p < 0.001$ for C vs I1 and C vs I2 ***Mean change in hip circumference after 12 months*** (in cm by ITT analysis) C: –0.1; I1: –3.2; I2: –6.2 $p < 0.01$ for C vs I1; $p < 0.001$ for C vs I2 ***Mean change in waist–hip ratio (x 100) after 12 months*** (by ITT analysis) C: –0.3; I1: –2.2; I2: –1.7 ns ***Mean change in HbA_{1c} (%) after 12 months*** (by ITT analysis) C: –0.29; I1: –0.56; I2: –0.34 ns ***Median change in fasting glucose (%) after 12 months*** (by ITT analysis) C: 0.0; I1: –1.8; I2: –2.3 ns	A total of 3 patients (1 from each group) were withdrawn from the study as a consequence of their SAEs. A further 16 patients (10 receiving sibutramine 15 mg, 2 receiving sibutramine 20 mg and 4 receiving placebo) were withdrawn because of non-SAEs Based on the numbers of patients who entered and completed, the numbers of withdrawals are: C: 64–46 = 18 I1: 69–50 = 19 I2: 62–49 = 13	***Study limitations, as noted by the study authors*** None ***Reviewer's comments*** No baseline data. Unclear which variables were used for statistical adjustment of between-group differences. No SDs or SEMs provided. Data are also available for ITT to endpoint (unclear why endpoint results are different from 12-month results) ***Sponsorship*** Knoll Pharmaceuticals

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Williams, 1999**[53]				***Median change in fasting insulin (%) after 12 months*** (by ITT analysis) C: –5.6; I1: –5.3; I2: –12.5 ns ***Median change in fasting C-peptide (%) after 12 months*** (by ITT analysis) C: –11.4; I1: –11.2; I2: –25.4 ns ***Median change in total cholesterol (%) after 12 months*** (by ITT analysis) C: –1.6; I1: 0.0; I2: –0.7 ns ***Median change in LDL-C (%) after 12 months*** (by ITT analysis) C: –6.3; I1: –1.6; I2: –5.0 ns ***Median change in HDL-C (%) after 12 months*** (by ITT analysis) C: 0.0; I1: 10.0; I2: 8.2 ns ***Median change in triglycerides (%) after 12 months*** (by ITT analysis) C: 5.2; I1: –14.3; I2: –9.3 ns ***Median change in uric acid (%) after 12 months*** (by ITT analysis) C: 7.7; I1: 0.0; I2: 0.0 $p < 0.05$ for I2 vs C ***% of 5% responders at endpoint vs C*** (OR (95% CI) by ITT analysis) C: 13%; I1: 46%; 6.8 (2.8 to 16.6); I2: 65%; 13.8 (5.5 to 34.7) ***% of 10% responders at endpoint*** (by ITT analysis) C: 0%; I1: 14%; I2: 17%		

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Williams, 1999**[53]				Although the overall treatment effect for the proportion of patients losing at least 10% of their baseline body weight was significant, there were no patients receiving placebo who lost 10% and therefore ORs could not be obtained to identify exact treatment differences There were statistically significant sex and treatment-by-sex interactions in the analysis of change in body weight from baseline, with females losing the most weight. Females in the sibutramine 20 mg group lost twice as much as both the males and females in the sibutramine 15 mg group Improvements in HbA_{1c}, fasting serum glucose and insulin, total and HDL-C and triglycerides were related to weight loss in sibutramine-treated patients; the greater the weight loss, the greater the improvement ***Safety results*** Overall, 65 patients (94%) in the sibutramine 15 mg treatment group, 60 patients (97%) in the sibutramine 20 mg treatment group and 60 patients (94%) in the placebo group reported a total of 427, 449 and 312 AEs, respectively. The most common AEs reported by patients treated with either 15 mg or 20 mg of sibutramine were asthenia, flu syndrome, headache, infection, accidental injury, pain, abdominal pain, back pain, hypertension, constipation, diarrhoea, nausea, arthralgia, dizziness, dry mouth, insomnia, bronchitis, pharyngitis and sweating A total of 8 patients reported SAEs, all of which involved hospitalisation There were few statistically significant differences between treatment groups in laboratory variables. None of the increases		

continued

(B) For RCTs from the manufacturer *contd*

Authors, year, country of origin, aim and design details	Inclusion/ exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Additional comments
contd **Williams, 1999**[53]				were assessed to be of clinical importance and reflected similar changes seen in previous trials with sibutramine ***Change from baseline to endpoint in mean seated SBP*** (mmHg) C: –0.2; I1: 4.4; I2: –1.5 $p < 0.05$ for I1 vs C ***Change from baseline to endpoint in mean seated DBP*** (mmHg) C: 0.5; I1: 3.3; I2: 0.4 $p < 0.05$ for I1 vs C PR and ECG HR were statistically significantly increased in the sibutramine groups compared with the placebo group. There was a treatment-by-hypertensive state interaction in PR, with non-hypertensive patients receiving placebo showing a reduction. In terms of cardiac conduction, there were decreases in PR, QRS and QT interval for all treatment groups with statistically significant decreases in PR interval for the sibutramine 20 mg group and statistically significant decreases in QT interval for both sibutramine groups. There were increases in QTc interval with no statistically significant differences between the groups		

AE, adverse events; AEE, adrenaline-stimulated energy expenditure; ANCOVA, analysis of covariance; BP, blood pressure; C, control group; DB, double blind; EE, energy expenditure; F/U, follow-up; HbA_{1c}, glycosolated haemoglobin concentration; HDL, high density lipoprotein; HR, heart rate; I, intervention group; I1, first intervention group; I2, second intervention group; I3, third intervention group; I4, fourth intervention group; I5, fifth intervention group; I6, sixth intervention group; LDL, low density lipoprotein; ns, not significant; OR, odds ratio; PP, per protocol; PR, pulse rate; REE, resting energy expenditure; RMR, resting metabolic rate; SAE, serious adverse event; SB, single blind; SEM, standard error of the mean

Appendix 4

Quality assessment table

(A) For published RCTs

Study	Apfelbaum *et al.*, 1999[46]	Bray *et al.*, 1999[41]	Cuellar *et al.*, 2000[48]	Fanghanel *et al.*, 2000[42]	Finer *et al.*, 2000[44]	Fujioka *et al.*, 2000[47]	Hanotin *et al.*, 1998[45]	Hansen *et al.*, 1999[38]	Seagle *et al.*, 1998[39]	Walsh *et al.*, 1999[43]	Weintraub *et al.*, 1991[40]
Method of generating sequence of randomisation	NS	T	T	T	NS	NS	NS	NS	NS	NS	NS
Concealed randomisation	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Selection criteria	Y	Y	Y	Y	Y	Y	Y	Y (brief)	Y	Y	Y
A priori power calculation	Y	NS	Y	Y	NR	Y	UC	NS	NS	NS	UC
Number of participants per group at baseline*	78:82	148:149:151: 150:152:146:151	35:34	54:55	44:47	86:89	114:112	18:14	16:17:16	9:10	20:19:21
Baseline comparability	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Intended identical treatment (apart from study interventions)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Attempt to blind patients	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Attempt to blind carers	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC
Attempt to blind outcome assessors	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC
Check to what extent blinding was successful for patients/carers/assessors	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all	NS for all
Description of statistical methods used	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measures of central tendency and variance	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Adjustment for baseline imbalance	NA	NS	NS	NA	NA	NA	NA	NA	NA	NA	NA
Methods for dealing with missing data described	Y	Y	Y	Y	Y	Y	Y	N	N	NA	N
ITT analysis	Y	Y	Y	Y	Y	Y	Y	N	N	NA	NS
Withdrawals reported	Y*	Y*	Y*	Y[a]	Y*	Y*	Y*	Y[b]	Y[b]	NA	Y*
Patient adherence assessed	Y	NS	Y	Y	Y (diet)	NS	Y	NS	Y (assessed but results not reported)	Y	Y (drugs)

(B) For RCTs from the manufacturer

Study	Wirth, 1998[49]	Smith, 1994[50]	James, 1999[51]	Rissanen, 1998[52]	Williams, 1999[53]
Method of generating sequence of randomisation	NS	NS	NS	NS	NS
Concealed randomisation	Y	Y	Y	Y	Y
Selection criteria	Y	Y (brief)	Y	Y	Y
A priori power calculation	NS	NS	NS	NS	NS
Number of participants per group at baseline*	201:395:405	163:161:161	115:352	122:114	64:69:62
Baseline comparability	N	N	N	N	N
Intended identical treatment (apart from study interventions)	Y	Y	Y	Y	Y
Attempt to blind patients	Y	Y	Y	Y	Y
Attempt to blind carers	UC	UC	UC	UC	UC
Attempt to blind outcome assessors	UC	UC	UC	UC	UC
Check to what extent blinding was successful for patients/carers/assessors	NS for all	NS for all	NS for all	NS for all	NS for all
Description of statistical methods used	Y	Y	Y	Y	Y
Measures of central tendency and variance	N	N	N	N	N
Adjustment for baseline imbalance	NS	NS	NS	NS	NS
Methods for dealing with missing data described	Y	Y	N	N	Y
ITT analysis	Y	Y	NS	Y	Y
Withdrawals reported	Y[a]	Y*	Y*	Y*	Y*
Patient adherence assessed	NS	NS	NS	NS	NS

NS, not stated; T, true randomisation; Y, yes; NR, calculated numbers not recruited; UC, unclear; N, no; NA, not applicable; Y, numbers of withdrawals reported per group and with reason; Y[a], numbers reported per group but not with reason; Y[b], numbers reported according to reason, but not per group*

**Number in control group at baseline: number in intervention group at baseline*

Appendix 5

Data extraction table for economic evaluations from the manufacturer

Author, year, country of origin, type of evaluation and currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
BASF Pharma/Knoll, 2000[54] ***Country*** UK ***Type of economic evaluation*** Cost–utility analysis ***Currency*** British £	***Intervention*** The main model was based on two placebo-controlled trials, where the drug regimen was combined with a dietary and exercise programme. Sibutramine-treated patients received 10 mg/day or 15 mg/day[50,51] ***Outcomes*** Cost/QALY gained	***Efficacy data*** – Effectiveness data were based on two studies[50,51] – CHD risk: work undertaken by BASF Pharma utilising the results from reported studies together with the Framingham equation – Diabetes risk: 3 published studies, relating weight loss to diabetes risk, were used[72–74] – QoL gained from sibutramine-induced weight loss was based on QoL information from 4 studies using SF-36.[57] The SF-36 results were converted to utility scores using the algorithm developed and validated by Brazier *et al.* (1998).[75] Regression techniques were used to estimate the relationship between utility gain and weight loss for sibutramine and placebo separately	The patient group employed was 1000 patients with BMI > 30 kg/m^2 who were free of co-morbidities and complications at the beginning of the modelling period The model was built around 3 elements: 1. the effect of sibutramine-induced weight loss on CHD risk 2. the effect of sibutramine-induced weight loss on the incidence of diabetes 3. the direct effect of sibutramine-induced weight loss on QoL The cost-effectiveness of sibutramine in each element was estimated separately, calculating the cost/QALY gained It was assumed that no patient would maintain any weight loss at 5 years Patients had to fulfil 3 criteria in order to continue for a full year of therapy: 1. loss of 2 kg after 4 weeks of treatment 2. loss of 5% of initial weight after 12 weeks of treatment 3. those not fulfilling (1) or (2) were prescribed a higher dose for 3 months (15 mg/day)	***Effectiveness***: The QoL coefficient for sibutramine was 0.00185 per kg lost (95% CI, 0.00048 to 0.00322) and for placebo 0.00142 (95% CI, 0.00058 to 0.00341) ***Proportions for responders***: Criteria 1 and 2 (10 mg): 39.1% Criteria 1 (10 mg) + 3 (15 mg): 4.4% Criterion 3 (15 mg): 8.7% ***Proportions for non-responders***: Criteria 1 (yes) + 2 + 3: 16.1% Criteria 1 + 3: 31.7% ***CHD risk***: The cost/QALY gained through CHD reduction alone: £42,000 ***Diabetes risk***: The cost/QALY gained through diabetes incidence reduction alone: £77,000 ***QoL***: Utility results combined with weight loss and weight regain evidence from trials produced an estimated cost/QALY from weight loss alone: £19,000 ***Combined cost/QALY***: £10,500 ***Sensitivity analysis***: Outcomes of the sensitivity analysis range from £3200 (monitoring costs incurred after 2 years by placebo group) to £16,700 (lower utility gained per kg lost) The single worst case scenario (high regain, low utilities per kg, include all monitoring, low diabetic prescribing	The model was tested for its sensitivity to the following variables incorporated in the model: – slope of regain curve – utility per kg lost – monitoring costs after 12 months – monitoring costs for drop-outs – prescribing costs of diabetes – inclusion of effects on CHD during years 2–5 – inclusion of effects on diabetes during years 2–5 – diabetes QALY multiplier – drug price	QALY scores for the sample population were adjusted from higher initial scores than those found by Kind *et al.* (1998) in the general population.[59] The validity of the results is highly dependent on QALY estimates and the methods used to derive them Concerns regarding this study: – methods used to derive QALYs were not direct (different populations for effectiveness results and QALY estimates) – cost/QALY results are very sensitive to QALY estimates – side-effects and associated costs are not included in the analysis – QALY gains per person from sibutramine are very small and it is uncertain whether they are clinically significant – uncertain whether all available trial data were used for estimation of QALYs, or a selection – not all co-morbidities are included because the necessary information was not available – authors do not explain why the starting utility of the obese cohort was significantly higher than the age-related utility data from Kind *et al.* (1998),[59] which was based on a survey of the general population (n = 3381)

continued

Author, year, country of origin, type of evaluation and currency	Interventions and main clinical outcomes	Sources of data	Methods and perspective	Results	Sensitivity analysis	Additional comments
contd BASF Pharma/Knoll, 2000[54]		***Cost data*** – The cost of sibutramine was £35 per month for the 10 mg dose and £39.09 for the 15 mg dose – Diabetes costs were derived from Hughes *et al.* (1999)[76] Cost assumptions: – Sibutramine-treated patients incur a monthly cost for as long as they are on treatment (maximum duration 1 year) – Drug cost as above – Patients receive 1 GP consultation per month in the year of treatment. Thereafter (years 2–5) responders continue to receive advice and monitoring through 1 practice nurse consultation per month	and had to lose 5% of initial weight Costs were discounted at 6% and benefits at 1.5% following Treasury recommendations	offsets, no QALY multiplier for diabetics, no continued benefit after year 1 for either CHD or diabetes) results in £35,200 per QALY gained The single best case scenario (low regain, high utilities per kg, exclude monitoring of sibutramine failures, high diabetic prescribing offsets, use 0.95 QALY multiplier for diabetics, assume continued benefit after year 1 for both CHD and diabetes) results in £5700 per QALY gained		

GP, general practitioner

Appendix 6

Quality assessment table for economic evaluations

Study	BASF Pharma/Knoll[54]
Well-defined question	Properly addressed
Comprehensive description of alternatives	Properly addressed
Effectiveness established	Unknown
Relevant costs and consequences identified	Properly addressed
Costs and consequences measured accurately	Properly addressed
Costs and consequences valued credibly	Properly addressed
Costs and consequences adjusted for differential timing	Properly addressed
Incremental analysis of costs and consequences	Not properly addressed
Allowance made for uncertainty in estimates of costs and consequences	Properly addressed
Results/discussion included all issues of concern to users	Properly addressed

Appendix 7

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ISSN 1366-5278